

Thomas A. Ban: Neuropsychopharmacology in Historical Perspective

Collated 43

Volume 3

**Recollections of the History of Neuropsychopharmacology Through
Interviews Conducted by William E. Bunney, Jr. (2016)**

Edited by Peter R. Martin

International Network for the History of Neuropsychopharmacology

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**RECOLLECTIONS OF THE HISTORY OF
NEUROPSYCHOPHARMACOLOGY THROUGH INTERVIEWS
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William E. Bunney, Jr. (circa 1980)

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PREFACE

This volume is the third of the Educational E-Books from the International Network for the History of Neuropsychopharmacology (INHN) on *Recollections of the History of Neuropsychopharmacology through Interviews* conducted by 1 of the 66 interviewers of the oral history series (OHS) of the American College of Neuropsychopharmacology (ACNP). The first volume of the INHN series includes the 37 interviews conducted by Leo E. Hollister and the second, the 56 interviews conducted by Thomas A. Ban.

An Oral History of Neuropsychopharmacology - The First 50 Years - Peer Interviews is a series of 10 volumes (Ban 2011). It is based on the transcripts of 235 videotaped interviews with 213 clinicians and basic scientists who contributed to the field during the first epoch of its development. The original collection of videotapes is stored in the ACNP Archives in Los Angeles (California, USA) and is accessible on the ACNP website.

The text of the transcripts in the OHS and the text of the videotapes are not identical. To render the original transcripts comprehensible and to clarify ambiguous information in the interviews, the transcripts of the videotapes were edited. To ascertain that the edited transcripts express interviewees' contributions and thoughts as closely as possible, interviewees were allowed to correct and, if necessary, revise the text (Ban 2011; Blackwell 2011a&b; Fink 2011; Gershon 2011; Katz 2011; Kleber 2011; Levine 2011; Salzman 2011; Shorter 2011; Sulser 2011). Furthermore, to sort out the great variety of information on the videotapes, each transcript was assigned to one of ten volumes, each volume dedicated to a different area of research. In each volume, the story of neuropsychopharmacology is told from a different vantage point (Ban 2011).

This volume is a compendium of interviews conducted by William E. Bunney, Jr. in the OHS of ACNP. The text is based but not identical with the edited interviews in the OHS. It is the result of a further edit carried out with the objective to overcome the differences in editing style of the different volume editors in OHS and improve readability as necessary.

Bunney was primary interviewer for 8 of the 235 interviews in this series from which two, the interviews with Louis A. Gottshalk and Heinz Lehmann were presented in *Volume One – Starting Up*, edited by Edward Shorter; one, the interview with J. Christian Gillin in *Volume Two – Neurophysiology*, edited by Max Fink; two, Arvid Carlsson and Salomon Z. Langer in *Volume Three – Neuropharmacology*, edited by Fridolin Sulser; another two, the interviews with Joseph T. Coyle and Ellen Frank in *Volume 8 – Diverse Topics*, edited by Carl Salzman; and one, the interview with Thomas A. Ban in *Volume 9 – Update*, edited by Barry Blackwell. The Bunney-conducted interviews provide a valuable perspective by virtue of the questions he posed and the stature of the neuropharmacologists interviewed. To offer the reader the opportunity to hear Bunney's own voice, one interview of Bunney, himself, conducted by Thomas A. Ban (December 10, 2001), originally presented in *Volume 9* of OHS, is included to complete this E-Book.

This Preface is not intended to summarize, nor can it do justice to Bunney's many contributions to neuropsychopharmacology and biological psychiatry throughout his long and influential career.

To help the reader better understand the scope of Bunney's academic life and his substantial influence on the field of neuropsychopharmacology, I have included a recently updated version of Bunney's curriculum vitae (Appendix 1) and an outline of his major scientific contributions (Appendix 2). My goal for this Preface is to provide a few personal vignettes of Bunney and some impressions of his influence since the early 1980s, a period during which I have had the opportunity to observe this field.

I first met Dr. Bunney (everyone called him "Biff"), in the fall of 1980, in the Clinical Center of the National Institutes of Health (NIH) in Bethesda, Maryland when I attended a seminar he regularly organized and chaired as Chief of the Biological Psychiatry Branch of the National Institute of Mental Health. I had just arrived from my Psychiatry Residency at the University of Toronto to work with Mike Ebert and Irv Kopin in the Laboratory of Clinical Science and was just getting to know my way around Building 10. The talks organized by Bunney were usually very informative and a useful way for a newcomer to begin to understand what was active and exciting in the Intramural Program of NIMH and to get to know the up and coming contributors of biological psychiatry. Many of the most famous names in the field whose work I had seen in the literature were in the audience and the lectures were truly stimulating. My first impression of Dr. Bunney was that he was somehow different from everyone else in the room. He was dressed like a banker—very elegant in white shirt, conservative tie, and dark blue suit—while everyone else was in shirtsleeves, khakis, Topsiders, with only the occasional tie, mostly at half-mast.

Bunney's introductions were concise, but to the point, and he never failed to mention the number of peer-reviewed publications on the speaker's curriculum vitae (clearly implying the more publications the better). Dr. Bunney was clearly a man who managed science and scientists with aplomb! His style of research at NIMH was leadership of research teams wherein carefully selected patients were extensively monitored using clinical rating scales and their body fluids were collected and subsequently analyzed for concentrations of biological compounds to seek a better understanding of the underlying psychiatric illnesses and response to treatment with neuropsychopharmacological agents.

Although I never knew Dr. Bunney personally, I have followed his career and contributions from my first days at NIMH. (An interesting coincidence was that Blynn Garland, who would soon become Biff's wife, was one of the many people I met when I first moved into the Promenade, an immense apartment building down the street from the NIH where a number of the new arrivals to Bethesda lived.) Somehow I felt I knew Dr. Bunney via all his colleagues with whom I became acquainted over the years. It is testimony to Bunney's profound influence in the Intramural Program of NIMH that the vast majority of investigators that I encountered during my years at NIMH/NIAAA were in some way linked to "Biff," either as his trainee or collaborator. When reviewing his curriculum vitae it is rather remarkable that he co-authored scientific publications with many of the leaders of the Intramural Program of NIMH and of American academic psychiatry and neuroscience. Following is a list of just a few of Bunney's co-authors whom I met during the early 1980s in the corridors of Building 10 at NIMH in Bethesda or at the scientific meetings we all attended: Jim Ballenger, David Behar, Lavonne Brown, Monte Buchsbaum, Martin Cohen, Robert Cohen, Dieter Naber, Neal Cutler, Mike Ebert, Blynn Garland, Elliot Gershon, Chris Gillin, Phil Gold, Lynne Goldin, Fred Goodwin, David Janowsky, David Jimerson,

Marion Kafka, Ned Kalin, Walt Kaye, Bob Kessler, Joel Kleinman, Charles Lake, Markku Linnoila, Ron Manning, Wally Mendelson, Dennis Murphy, Phil Ninan, John Nurnburger, Agu Pert, Candace Pert, Dave Pickar, Linda Porrino, Bob Post, Judy Rapoport, Dave Rubinow, Mika Scheinin, Larry Siever, John Tallman, Tom Uhde, Dan van Kammen, Tom Wehr, Dan Weinberger, Herb Weingartner, and Richard Wyatt. Clearly, this is only a portion of all the psychiatrists and neuroscientist with whom Dr. Bunney has collaborated throughout his long career which continued into its next phase when he moved to the University of California Irvine as Chair of the Department of Psychiatry.

It is interesting to read in Bunney's interview with Tom Ban about his early interests, a struggle between science and literature and the ministry and his passion for writing poetry and his dream to write the great American novel. Fortunately, instead of a life of skiing and becoming a novelist, he chose psychiatric training at Yale, followed by an important career in biological psychiatry and neuroscience. His breadth of involvement both at NIMH/NIDA and the University of California-Irvine, where he even now occupies a leadership position, reflect a man who has scope, has stayed connected to the latest technology and could recruit the finest scientists to help his vision become a reality.

Bunney considers his major contributions to be studies from his time at NIMH which helped launch the use of lithium in the United States, identification of biomarkers for suicidality and demonstration that norepinephrine was critical in the pathophysiology of depressive reactions; and more recently, at Irvine, where he and colleagues provided the first direct evidence of circadian patterns of gene expression in human brain and abnormal patterns in major depressive disorder as well as evidence to suggest that rapid-acting antidepressants may act on Clock Genes.

Much of Bunney's work made a real difference in patients' lives and this should never be forgotten. As one example of the relevance of Bunney's contribution, I would like to mention the personal observations of a good friend, who now lives a very full and productive life as a family man and a psychiatrist. My friend gives considerable credit to insights he gained during his psychiatric residency after reading Bunney's work from the Intramural NIMH, investigating the neurobiology of the "switch process" in bipolar illness:

"I found the work of Dr. Bunney and his colleagues a great source of reassurance after experiencing repeated psychiatric hospitalizations within days of starting tricyclic and later SSRI antidepressant medications. It took far too long for us to urge caution in the use of antidepressants for bipolar patients. Although the current guidelines for bipolar treatment reflect Bunney's work of 45 years ago, it is alarming that so many psychiatrists still fail to recognize the role these drugs may play in mixed bipolar states."

In closing, I would like to sincerely thank Ronnie D. Wilkins, Ed. D., CAE, the Executive Director of the American College of Neuropsychopharmacology, for allowing me to present this material based on nine interviews conducted (eight by William E. Bunney and one by Thomas A. Ban) for the OHS of ACNP and initially published under the imprimatur of the College.

Peter R. Martin

Nashville, Tennessee, U.S.A.

October 26, 2016

1. THOMAS A. BAN

WB: I'm William Bunney and I'm interviewing Dr. Thomas Ban*. It is December 10, 2007. We are at the annual meeting of ACNP in Boca Raton. Tom, could you begin by telling us something about your background, early interests, and how did you get started in medicine?

TB: I was born in 1929, in Budapest, Hungary in a middle class family. As far as I can remember, I was interested in books and in my teens I was a voracious reader, wrote poems, short stories and even a book. At age sixteen, I won a student competition award for an essay on the transformation of the 18th century novel in the early 20th century; I attributed it to the influence of Freud and psychoanalysis. I was encouraged to prepare for a career in literature. But, my world that had collapsed with World War II was changing again. Hungary became a "people's democracy," and I thought it would be safer to enter medical school.

WB: What about college?

TB: We went straight to university from high school, but I had the equivalent of a college education by auditing courses in history and philosophy.

WB: Where did you go to university?

TB: The Medical School in Budapest, in 1948. It was the old Semmelweis Medical University, only the name had changed.

WB: When did you get your medical degree?

TB: In 1954.

WB: Did you do any research during the time you were in medical school?

TB: No, but in the fourth year, with a classmate of mine, we received First Prize for our essay on *Post-traumatic epilepsy*. It was also during that year I became interested in psychiatry. I was fascinated by the lectures of Gyula Nyiro, our professor. He was a structural psychopathologist, who viewed mental symptoms as abnormalities in the processing of signals between and across

*Thomas A Ban was born in Budapest, Hungary, in 1929. He was initially trained in psychiatry at the National Institute for Nervous and Mental Diseases in Budapest. When he left Hungary in 1956, he obtained a fellowship at the Montreal Neurological Institute, followed by further psychiatric training at McGill University. During his time at McGill, he conducted research in psychopharmacology and conditioning in psychiatry. In 1976, he moved to Vanderbilt University to direct the clinical division of the Tennessee Neuropsychiatric Institute. He was interviewed in Boca Raton, Florida on December 10, 2007.

different levels of three mental structures corresponding with the three neuronal component of the reflex.

WB: When you got out of medical school, what did you do?

TB: I got a job as a junior physician at the National Institute of Nervous and Mental Diseases.

WB: What about residency?

TB: We did not have residency training. I started on one of the services of the Institute where patients with “neuroses,” called anxiety disorders today, were treated.

WB: How were they treated?

TB: Most of them were given tonics, like Arsotonin and Strychnotonin by daily subcutaneous injection. We did psychotherapy, quite frequently with chemically-induced abreactions, and hypnosis in some patients.

WB: How long were you on that service?

TB: For six months. Then, I was assigned to one of the admission services at the Institute.

WB: What kind of treatments did you have there?

TB: We had a morphine-scopolamine combination for controlling agitated and violent patients, and a phenobarbital and bromide combination, BromSevenal, for sedation. We also used paraldehyde and chloral hydrate. We treated schizophrenia with insulin coma, depression with tincture of opiate and both with ECT. Then, sometime in the spring of 1955, we had our first patients on chlorpromazine and reserpine. We also had a couple of patients on lithium.

WB: You used lithium in the mid-1950s?

TB: Yes, in 1955. György Sándor, my service chief, followed the literature very closely. I remember having our lithium supply prepared in the pharmacy and the Institute had a flame photometer to monitor plasma levels.

WB: Did he publish?

TB: Dr. Sándor was not interested in writing papers but, to my surprise, he was open to my suggestion, when the new drugs appeared, to start a quarterly Digest for the Institute to keep everyone abreast of developments.

WB: Did you publish any papers in Hungary?

TB: I published three brief reviews. One was on the development of the diagnostic concept of neurosis, another on the story of “BromSevenal” and the third was an overview of the history of psychiatric nursing.

WB: It seems that you got your first experience with the new drugs in Hungary?

TB: I had my first exposure to some of the new drugs.

WB: Did you use Marsilid (iproniazid) in Hungary?

TB: Marsilid was used only at our special service for tubercular patients.

WB: Was it used in depression?

TB: No, it was only used in the treatment of tuberculosis.

WB: When did you leave Hungary?

TB: In November 1956, after the revolution.

WB: You went to Montreal?

TB: Before Montreal, I spent a few weeks in Vienna at the University Clinic of Hans Hoff. started with my fellowship at the Montreal Neurological Institute (MNI), in early January 1957.

WB: How did you get that fellowship?

TB: I wrote to Wilder Penfield and told him about my essay on post-traumatic epilepsy. I also told him that I would like to further my training in his Institute. I was familiar with the monograph he wrote with Herbert Jasper on *Temporal Lobe Epilepsy* and *The Functional Anatomy of the Brain* from editing our Digest. I did not expect he would respond, but he did, and even contacted the Canadian authorities to issue me an immigrant visa. In less than two months after I crossed the Hungarian-Austrian border, I was attending Francis McNaughton's epilepsy clinics, and Herbert Jasper's research rounds at the MNI. In June 1957, I left for Halifax to do a rotating internship at the Victoria General Hospital of Dalhousie University. A year later, I passed the Canadian Medical Council examinations, which allowed me to apply for a license to practice medicine.

WB: How did you get to work with Dr. Lehmann?

TB: I was accepted in McGill's residency training program and was assigned for my first year to the Verdun Protestant Hospital (VPH), a large psychiatric hospital affiliated with McGill that served the English speaking population of the city, where Dr. Lehmann was clinical director. I met Dr. Lehmann for the first time on the 1st of July 1958 and, a few days later, I started to work with him on some of his research projects.

WB: How did this happen?

TB: Doctor Lehmann asked whether any of us new residents would be interested to work with him on some of his projects.

WB: How many of you were interested?

TB: From the six of us, only me. But later on, some of the others got on board.

WB: What was your first project?

TB: I got involved with several projects simultaneously. In one, my task was simply to stay with some of my fellow residents and other psychiatrists who were given psilocybin.

WB: Psilocybin?

TB: At that time, it was thought educational for those dealing with psychotic patients to get an idea about what patients were experiencing.

WB: What about the other projects?

TB: In another project, we studied the effects of prototype CNS acting drugs, like dextroamphetamine, secobarbital, chlorpromazine, prochlorperazine, imipramine, and lysergic acid on enzyme functions and on biological systems of low complexity, including urease, firefly lantern extracts, proteus bacteria, oat seedlings, the feeding reflex of hydra, and dandelion sleep movements. And, in a third, we studied the effects of phencyclidine (Sernyl), in different doses and in different diagnoses, as well as in a few normal subjects. Dr. Lehmann received a supply of Sernyl from Parke Davis to find out whether it would be suitable for the facilitation of psychotherapy. It was not, but I became interested in the compound and it did not take me long to recognize it was a substance that could change how one experienced oneself and the world. Its effects were distinctly different from psilocybin. Just from curiosity, I also gave Sernyl with a friend to a few rats. To our amusement, the animals started to walk backward!

WB: Did you publish your findings?

TB: We had two papers on Sernyl: one, in 1961, in the *Canadian Psychiatric Association Journal*, and another, a few years later, in the proceedings of the fourth CINP Congress. My first paper on Sernyl, and my first paper based on my conditioning research appeared almost simultaneously. They were really my first “scientific” publications.

WB: How did you get involved in conditioning?

TB: At the time I started my residency at McGill, we were still expected to prepare a thesis, based on some research, but mainly a literature review, to get our diploma in psychiatry. Since VPH had a conditioning laboratory, Dr. Lehmann, who was also my thesis supervisor, encouraged me to select a topic related to conditioning.

WB: When did you get your Diploma from McGill?

TB: In 1960, and I got it with distinction. Furthermore, on the recommendation of my examiners, my thesis was published with some modifications under the title, *Conditioning and Psychiatry*, by Aldine, in the United States, in 1964, and by Unwin, in the United Kingdom, in 1965. I had a Forward written by Horsley Gantt, the American disciple of Pavlov. Dr. Gantt apparently liked my thesis and invited me to join his Society, the Pavlovian Society of North America. A few years later, in 1966, at the World Congress of Psychiatry in Madrid, I also became one of the founders of the Collegium Internationale Activitatis Nervosae Superioris (CIANS), an international society of people involved in conditioning research.

WB: Does that College still exist?

TB: Yes, but after Dr Gantt died, it was no longer the same College.

WB: When did he die?

TB: In 1980. He got seriously ill just a few weeks before a CIANS Congress in Milan and passed away soon after.

WB: Would you like to say something about your research in conditioning?

TB: From reviewing the literature, I got the idea that behavioral conditioned reflex (CR) variables might provide a bridge between psychopathology and neurophysiology. So, as soon as the thesis was completed, I developed a diagnostic test procedure based on the conditioning method using the eyelid closure technique. Then, in the 1960s, in collaboration with Drs. Lehmann and Bishan Saxena, a psychologist, we developed a conditioning test battery, the Verdun Conditioning Test Battery (VCTB), using several techniques to study psychopathological mechanisms and psychopharmacological effects. We also developed, in the 1960s, a psychometric test battery, the Verdun Psychometric Battery (VPTB) that included several perceptual, psychomotor, and other tests. Our interest was identifying predictors of treatment response to psychotropic drugs with the employment of these batteries. In the early 1970s, we published our findings in a monograph, *Experimental Approaches to Psychiatric Diagnosis*. Although I did not continue with research in conditioning after the mid-1970s, all through the years I have been thinking of resuming it. To acquire a CR is an innate property of the brain and our studies had indicated that CR variables, like acquisition, extinction, differentiation, reversal, etc., might provide a key to the understanding of the pathophysiology of abnormal mental functioning.

WB: What did you do after your residency?

TB: My residency was cut short because I was promoted from the first to fourth year, and in 1959, I became the junior member of Cameron's research team on "psychic driving." Ewen Cameron was chairman of psychiatry at McGill. He was one of the Nuremberg-psychiatrists and a past president of the American Psychiatric Association (APA).

WB: Would you like to say something about the research?

TB: The idea behind Cameron's research was that by wiping out all memories, one would also wipe out pathological patterns in the brain, and one might be able to rebuild the psyche anew. We also explored the possibility that it might be sufficient just to disorganize memories. For wiping out memories, we used regressive ECT, which Cameron referred to as "depatterning"; for disorganizing memories, we used psychomimetic drugs and sensory isolation; and for rebuilding, repetition of verbal signal therapy, which he referred to as "psychic driving." As the junior member of the team, I had to do whatever needed to be done, but my specific responsibility was the monitoring of changes in psychophysiological measures and CR variables. Today, what we did might sound rather unsophisticated, but it corresponded with the kind of research people did in those years. In our "sleep room," for example, where most of the research was done, in one bed a patient was treated by our team with regressive ECT and in the next bed, a patient was treated with "anaclitic therapy" by another research team, in which, grown-ups were mothered like babies. For me, still pretty much a foreigner in this new world, both treatments were rather strange, but the rationale for our experiment was at least as sound as the treatment used by the psychoanalytic group. In fact, we learned from our experiments that some patients with schizophrenia were not affected by sensory isolation, and also that wiped out obsessive-compulsive patterns re-emerge much sooner than memory returns. I left the team before it became public that the grant supporting our project came from the Society for Investigation of Human Ecology, a cover organization for the CIA. Cameron was vilified by the press, resigned and died shortly thereafter, while mountain climbing. It was never completely clear whether he knew some of the money was from the CIA. I certainly did not. But even if he had known, I don't think he would have cared. Funds from the CIA were just as good as funds from anywhere else. He was interested in what he was doing and dedicated to help his patients.

WB: When did you get involved in drug studies?

TB: In the late 1950s. And, then, in the early 1960s, Jon Cole suggested to Dr. Lehmann to apply for a grant that would support an early clinical drug evaluation unit (ECDEU) at VPH, which, by

that time, was renamed Douglas Hospital (DH). Lehmann was hesitant to pursue the matter, but when I expressed interest and willingness to direct the unit, we applied and our unit became one of the first in the program. So, during the 1960s and 1970s, we studied virtually all the psychotropic drugs that became available for clinical use in Canada and United States and many others that never made it. I was told by Bill Guy, who was analyzing our data at the Biometric Laboratory of George Washington University, that we studied two or three times as many drugs as the other units in the program.

WB: Which were the drugs you studied?

TB: I think cyclopentimine, a sympathomimetic alkylamine, and RP 8228, a phenylpiperidyl acetoxymethane, were the first drugs we published on.

WB: This was in the early 1960s?

TB: We studied these drugs in the late 1950s, before we set up our early clinical drug evaluation unit and published our findings in the early 1960s. When I first became involved with clinical investigations, it was a commonly held belief that inducing extrapyramidal signs (EPS) was a prerequisite for responding to neuroleptics. The newer neuroleptics induced more frequent and severe EPS, but contrary to the mainstream, in our hands, none of the newer drugs was any better than chlorpromazine. In fact, chlorpromazine appeared to be a more reliable treatment than any of its competitors. We conducted studies with “incisive neuroleptics,” like prochlorperazine and thioproperazine, which were more potent on mg per kg basis in inducing both therapeutic effects and EPS and also with “sedative neuroleptics,” like methotrimeprazine, referred to as levomepromazine and chlorprothixene. Our findings with these drugs did not change our impression; “incisive neuroleptics” did not offer any real advantage over “sedative neuroleptics.” There were differences in adverse effects, but not in therapeutic effects. In our conditioning studies, the effect of neuroleptics on the extinction of the orienting reflex seemed to be a more reliable predictor of whether a neuroleptic would work than the appearance of EPS.

WB: What about your findings with antidepressants?

TB: We were among the first to report on clinical findings with desipramine, the demethylated metabolite of imipramine, the first selective norepinephrine (NE) inhibitor. In our study, desipramine did not seem to be a better antidepressant than imipramine or amitriptyline, the two antidepressants available at the time. So, we were somewhat puzzled when, a few years later, the catecholamine hypothesis of affective disorder was formulated. If the hypothesis was correct,

desipramine should have been better than imipramine, the parent substance that had an effect on both 5HT and NE re-uptake. We were also involved, in the early 1960s, in studying trimipramine, a tricyclic compound which has no effect either on NE or 5-HT reuptake. It was just as good an antidepressant as any of the NE and/or 5-HT uptake inhibitors. Again, we were contrary to the mainstream. Those were exciting times, learning about these new drugs. We studied several tricyclic antidepressants; amitriptyline was more sedative than imipramine; desipramine had less anticholinergic side effects; trimipramine could safely be administered in combination with monoamine oxidase inhibitors; doxepin did not cause cardiac death in overdose, etc.

WB: You didn't have rating scales at the time?

TB: We used two scales from the very beginning, the Verdun Target Symptom Rating Scale and the Verdun Depression Scale, developed by Dr. Lehmann, in collaboration with Charlie Cahn and Roger deVerteulle, for the first North American study of imipramine. We also used a comprehensive Psychopathological Symptom Check List (PSCL). But, for me, changes in the psychopathological symptom profile of individual patients were far more informative than changes in rating scale scores. In the early 1980s, to get more information than from conventional scales, like the Brief Psychiatric Rating Scale and Hamilton Depression Scale, we (in collaboration with Bill Guy) translated the AMDP and AGP Systems Manuals for the Assessment and Documentation of Psychopathology that were used in German speaking countries. At the same time, with a group of Italian psychiatrists in Pisa, we updated the ECDEU Assessment Manual, a collection of rating scales for use in clinical investigations, prepared by Guy and Bonato, in 1970.

WB: You were involved in the clinical development of how many psychotropic drugs?

TB: Probably about 90. It would be difficult to recall by name all the drugs we studied. The list includes benzquinamide, butaclamol, butaperazine, clobazam, clomacran, clomipramine, clovoxamine, fluspirilene, flutroline, maprotiline, mesoridazine, mianserine, molindone, nomifensine, pimozone, propericiazine, viloxazine, and many others.

WB: Any observations or findings you would like to share?

TB: We noted carbamazepine's effect on mood in the mid 1960s, while studying it in epileptics; we had shown that nylidrine potentiates the effect of phenothiazines; we recognized the potential use of metronidazole in the treatment of alcoholism, of propranolol in organic agitation, and of naltrexone in controlling hallucinations in chronic schizophrenia; and we replicated Art Prange's findings with TRH in depression. In the late 1960s and early 1970s, we explored the possibility,

with Dr. V.A. Kral, of using a pharmacological load test, such as 5% carbon dioxide inhalation, and intravenous injection of methamphetamine or sodium amobarbital in the prediction of therapeutic response in elderly patients to prototype psychotropic drugs, like methylphenidate, meprobamate, amitriptyline, thioridazine, nicotinic acid, and fluoxymeterone. We had numerous statistically significant findings, but none of them was of clinical significance.

WB: So, you had a special project in psychogeriatrics.

TB: We had a NIMH grant to study psychotropic drugs in the aged, while I was with McGill, and I continued with clinical investigations in the elderly during the Vanderbilt years. We were among the first, in the 1980s, to report favorable effects with nimodipine, a calcium channel blocker and choline alphasphosphate, a cholinomimetic substance in old age dementias. We had done several studies with Ateroid (glycosoaminoglycan polysulfate), a substance with heparinoid activity and I noted that it helped some patients with Alzheimer's and also some patients with vascular dementia.

WB: Did you publish all these findings?

TB: We presented and published most of our findings. In the early 1960s, together with a few colleagues interested in clinical investigations with psychotropic drugs in the Province of Quebec, we founded the Quebec Psychopharmacological Research Association (QPRA), the predecessor of the Canadian College of Neuropsychopharmacology, that provided a forum to discuss research findings. The proceedings of most of the QPRA symposia were published and made available. It was at a QPRA symposium, where we presented our findings in the first North American studies with haloperidol and triperidol. And it was also at a QPRA symposium, where we presented our findings in the first North American studies with chlorprothixene and clopenthixol. We were involved in the early years in side effect reporting to both the Canadian Health Protection Branch and the FDA. We thought that communicating some of the side effects we encountered was sufficiently important that we organized a QPRA symposium dedicated to skin pigmentation and ophthalmological changes seen in patients treated with high doses of chlorpromazine over a long period of time. Another QPRA symposium dealt with thioridazine-induced cardiac conductance changes. Our EKG studies with thioridazine were triggered by a report on two fatalities in the *Canadian Medical Association Journal* in 1963, and our findings reported, in 1964, in the same journal indicated that thioridazine produces a dose dependent prolongation of the QT interval that could lead to ventricular fibrillation. It might be relevant for the historical record that at the request of Sandoz, the Swiss drug company that manufactured thioridazine, we invited M.H. Wendkos, a

cardiologist at the Coatesville Veterans Administration Hospital in the United States, to our QPRA symposium, and he argued that the EKG changes with thioridazine were due to “benign repolarization disturbances.”

WB: You worked with Heinz Lehmann until when?

TB: From 1958 to 1976, while I was in Montreal but our collaboration continued after I went to Nashville. I started as his resident, then I became his Co-Principal Investigator and when I was appointed Director of McGill’s Division of Psychopharmacology, he chaired our Board of Advisors. I think it was on his recommendation that I was asked to coordinate the Canadian Mental Health Association’s (CMHA) studies on *Nicotinic Acid in the Treatment of Schizophrenia*.

WB: Would you like to say something about those studies?

TB: It was a series of collaborative studies designed to replicate Abe Hoffer’s findings. But, as you probably know, we could not. Niacin was just not effective in the treatment of schizophrenia, regardless of whether it was given alone, or in combination with ascorbic acid or pyridoxine. There was no indication in our studies that niacin would augment the effect of neuroleptics, either in acute or in chronic schizophrenic patients. We did not have a single patient who markedly benefited. To stop the nicotinic acid craze, which affected psychiatry in Canada more than any other country because Hoffer practiced in Saskatoon, our findings were widely publicized. They also found their place in the *American Psychiatric Association’s Task Force Report on Megavitamin Treatment in Psychiatry*. I was a member of that Task Force; Morrie Lipton, a distinguished past president of ACNP, was chairman.

WB: You mentioned McGill’s Division of Psychopharmacology. When was that established?

TB: In 1971. It was the first Division of Psychopharmacology in a University Department of Psychiatry. It started as a network of clinical investigators in seven McGill affiliated hospitals.

WB: So, we are now in the 1970s?

TB: Yes. Just about the time that the Division was established, I became Head of the Canadian Reference Center of the International Reference Center Network on Psychotropic Drugs. The Network was a joint effort between the Division of Mental Health of WHO and NIMH, and it was coordinated by Alice Leeds from Washington. It was also the time, or might be a little bit later, that we started WHO’s first training program for teachers of psychopharmacology. It was initiated by Gaston Castellanos, an officer in WHO’s Division of Mental Health. We had several Fellows in that program annually from the early 1970s to the late 1980s. The first group of four Fellows

was from Latin America: Ronaldo Ucha Udabe from Argentina, Luis Vergara from Panama, Carlos Zoch from Costa Rica, and Luis Galvan from Mexico. They were followed by Torres-Ruiz from Mexico and Imaz from Argentina. I had Jüri Saarma, one of Kraepelin's successors as Chair of the Department of Psychiatry at the University of Tartu in Estonia, working with me for about a year with the Fellows. Soon after I moved to Nashville, the program moved with me, and we had three Fellows, one after the other, from Czechoslovakia. Two of them, Jan Liebiger and Eva Ceskova were to become professors of psychiatry, heads of university departments, after returning home, and one, Vaclav Filip, was to set up the first Clinical Research Organization (CRO) in that region. Then, we had Asano and Higano from Japan, Rudra Prakash from India, and Aitor Castillo from Peru. Among the last Fellows I had were Marek Jarema and Francois Ferrero. Marek was to become head and professor of one of the three psychiatric university clinics in Warsaw and Francois was to become head and professor of the Department of Psychiatry at the University of Geneva.

WB: Could you say something about your WHO program? What did the Fellows do?

TB: They participated in our activities and got experience in designing and conducting clinical drug studies, processing and analyzing data, and preparing reports.

WB: Did you keep contact with your Fellows after they left?

TB: I did, and developed research collaboration with most of them. In the late 1990s, we registered a research company for the clinical profiling of psychotropic drugs.

WB: When did you move to Vanderbilt?

TB: In 1976.

WB: What was your position at Vanderbilt?

TB: I went there as director of the clinical research division of the Tennessee Neuropsychiatric Institute, a research facility on the premises of an old state hospital. Then, when the Institute was declared a fire hazard and closed, I continued at Vanderbilt as a tenured professor in the Department of Psychiatry, until becoming emeritus in the mid-1990s. From the Vanderbilt period, I spent two years, from 1981 to 1983, on an extended sabbatical in Geneva.

WB: What did you do in Geneva?

TB: I was consultant in psychopharmacology to the Division of Mental Health of WHO. During my first year, we carried out a "consensus study" among opinion leaders to find out their agreement how to use psychotropic drugs. So, we asked 28 opinion leaders with representation from five

continents whether they agreed or disagreed with 32 treatment-related statements. We got a 100 percent consensus in response to four statements only. All opinion leaders agreed that neuroleptics are indicated in the manic phase of manic-depressive psychosis; that long acting, depot neuroleptics should be used in the maintenance therapy of chronic schizophrenic patients who are unreliable about taking their medication; that amitriptyline has sedative effects; and that intravenous benzodiazepines are the treatment of choice for controlling status epilepticus. After returning to Nashville, I remained involved in consensus research with Mitch Balter and Uhli Uhlenhuth, until Mitch's untimely death. Another project I initiated at WHO was the development of an international network of clinical investigators, or more correctly a network of clinical research units, for the study of psychotropic drugs. My idea was to create a self-supportive network from contracts with the drug industry for efficacy studies on new drugs, which would develop and implement a methodology for the clinical profiling of psychotropic drugs. Norman Sartorius seemed pleased with the idea of setting up the network and Sandoz was ready to sign our first contract. Bissy Odejide, one of my former WHO fellows, at the time a professor of psychiatry at the University of Ibadan, Nigeria, agreed to direct the new program with me as consultant, and in a whirlwind trip, I traveled around the world from Cairo to Tokyo and Buenos Aires to identify prospective lead investigators in the network. By the time I returned to Geneva, the project was dropped; I never learned who blocked the project. It would have provided for worldwide clinical development of psychotropic drugs, a database that could have prevented confounding marketing with education about psychotropic drugs and it might have generated feedback for pre-clinical research on developing rational treatments.

WB: Was there a central theme throughout your lifetime of research?

TB: The central theme of my research shifted during the years, from trying to find a common language for the pharmacodynamic action of psychotropic drugs and mental pathology, to trying to identify pharmacologically homogeneous populations within psychiatric diagnoses. The turning point was the publication of my text, *Psychopharmacology*.

WB: When was it published?

TB: It was published, in 1969, by Williams and Wilkins. I think it was the first book, in which psychopharmacology was presented as a discipline and not just therapy with psychotropic drugs. It was probably also the first book in which the development of psychotropic drugs is systematically reviewed from structure-activity relationships to clinical applications. The first part,

General Psychopharmacology, is based on the material discussed at an ACNP Workshop, “What Preclinical Information Does the Clinician Expect to Be Given Prior to Conducting a Clinical Trial,” for which I tabulated all the information, i.e. brochures we received from the pharmaceutical company before starting a study with their drugs; the second part, “Systematic Psychopharmacology,” is based on a series of papers, published in *Applied Therapeutics*, in which all the information I was able to access about different groups of drugs, e.g., phenothiazines, benzodiazepines, in clinical use are reviewed; and the third, “Applied Psychopharmacology,” on the notes I used in teaching pharmacotherapy to psychiatric residents at McGill. It was in the “Closing Remarks” of Psychopharmacology that I first recognized the need to resolve the pharmacological heterogeneity within the diagnostic groups for neuropsychopharmacology to progress.

WB: How did you go about it?

TB: First, I thought that one might replace old diagnostic presuppositions by new diagnostic concepts, built from new building blocks, based exclusively on biologic criteria. But, by the mid-1980s, I recognized that biological measures have not shown to be anything more than epiphenomena of mental illness, and pharmacokinetic differences contributed little to the differential effect of psychotropic drugs. So, in a paper published in 1987, I postulated that there is a clinical prerequisite for neuropsychopharmacological research; that the meaningfulness of biological, including psychopharmacological findings, depends upon whether they can be linked to a prior, valid diagnostic category based on psychopathology and psychiatric nosology.

WB: How did you get to this?

TB: I came across a paper by Frank Fish, a British professor of psychiatry, published in 1964 in *Encephale*, a French medical journal, in which, by re-classifying patients with schizophrenia using the method of Karl Leonhard, a German professor of psychiatry, he found a moderate to marked response to neuroleptics in more than 4 in 5 patients diagnosed as “affect-laden paraphrenia” - a sub-population of “unsystematic schizophrenia” characterized by delusions with intense emotional participation - and in less than 1 in 4 patients diagnosed as “systematic hebephrenia,” a subpopulation of “systematic schizophrenia.” Stimulated by Fish’s findings, we developed several instruments for identifying treatment responsive sub-populations that might be covered up by consensus-based diagnoses. These instruments include, *A Guide to Leonhard’s Classification of Chronic Schizophrenias (GUIDE)*, the *DCR (Diagnostic Criteria for Research) Budapest-*

Nashville for the Diagnosis and Classification of Functional Psychoses, an instrument created in collaboration with Bertalan Pethö's Hungarian team; *CODE-DD Composite Diagnostic Evaluation of Depressive Disorders*; and *CODE-HD Composite Diagnostic Evaluation of Hyperthymic Disorders*, developed in collaboration with Peter Gaszner, a Hungarian professor of psychiatry, while he was working with me in Nashville. *CODE-DD*, the prototype of the CODE System, was adopted and translated from English into Estonian, French, Hungarian, Italian, Polish, Portuguese, and Spanish.

WB: Would you like to say something about your findings?"

TB: Our findings with the *GUIDE* and the *DCR* showed that the significantly different therapeutic response to neuroleptics in the two classes of schizophrenia reported by Fish, and also by Christian Astrup, is not restricted to therapeutic effects but applies also to adverse reactions. In an analysis of our international survey of about 800 chronic hospitalized schizophrenic patients, we found that tardive dyskinesia (TD) occurred more than three times as frequently in patients diagnosed, "systematic schizophrenia," than in patients diagnosed "unsystematic schizophrenia." Since, in Fish's study, moderate to marked response to neuroleptics is more than three times as frequent in "unsystematic schizophrenias" than in "systematic schizophrenias," the inverse relationship between therapeutic effects and TD indicates that the two classes of schizophrenia are pharmacologically distinct. Findings with *CODE-DD* indicate that DSM-III-R's diagnostic concept of "major depression" is so broad that, using more stringent criteria, a large proportion of patients would not qualify for a depressive illness. In one study, from over 300 patients, only about one-third fulfilled *CODE-DD*'s criteria of "melancholia," characterized by unmotivated depressed mood, depressive evaluations, and lack of reactive mood changes. In another study of over 200 patients, less than one-fifth fulfilled Kurt Schneider's criteria of "vital depression," characterized by corporization, disturbance of vital balance, and feeling of loss of vitality. The discovery of the antidepressant effect of imipramine, as you know, was based on Roland Kuhn's findings in "vital depression." Our *CODE-DD* findings imply that those high prevalence rates of depression in epidemiological studies are irrelevant to neuropsychopharmacology. I had many discussions about our findings with Heinz Lehmann, before he passed away.

WB: He was a giant in the field. How old was he when he died?

TB: He was eighty eight.

WB: He was your mentor?

TB: I had two mentors. My first was Dr. Sandor, who introduced me into psychiatry, and my second mentor was Dr. Lehmann, who introduced me into psychopharmacology. As years passed, our working relationship evolved into a very close friendship.

WB: Before we run out of time, let me ask you a few specific questions. Where did the financial support for your research come from?

TB: NIMH, MRC (Medical Research Council) of Canada, the State of Tennessee, and from the drug industry. The development of CODE-DD was linked to the early clinical development of reboxetine and sponsored by Farmitalia supporting clinical investigations we conducted mainly with my former Fellows. By the 1990s, our research support from industry markedly decreased because I had no interest in participating in multi-center clinical investigations organized by CROs.

WB: Could you list what you think are your major findings?

TB: Well, I discovered that trazodone and reboxetine have antidepressant properties; that Ateroid might have therapeutic effects in old age dementias, but I don't consider those as major discoveries. My *Psychopharmacology* in the late 1960s, in which I systematically presented the action of psychotropic drugs at different levels, from molecular through neurophysiological and behavioral to translate pharmacological properties into clinical effects, I think was a major contribution that had an impact on the development of the field, even if that book is outdated by now and by and large forgotten. I consider my most important contribution the recognition of the pharmacological heterogeneity within psychiatric diagnoses and developing methodologies for identifying more homogeneous populations in terms of psychopathology and psychiatric nosology. I also consider our conditioning test battery for the study of psychopathology and psychotropic drug effects, a contribution.

WB: So, all your work has been clinical, not basic?

TB: The answer is yes, even if during the 1960s, I was involved in some preclinical research with Drs. Kato and Gozsy, in exploring the effects of psychotropic drugs on dextran-induced capillary permeability. I found it interesting that one could predict whether a substance is an antipsychotic or an antidepressant from its effect on dextran-induced capillary permeability. Of course, if anyone would have suggested testing a hypothesis that capillary permeability changes are the cause of depression or antidepressant effects, I would have been the first to object.

WB: Do you still see patients?

TB: I was seeing patients for well over forty years and used to pride myself that I had seen several times more patients than many practicing psychiatrists together, but my current activities don't leave me time to have even a part time practice.

WB: Tell me about the teaching experiences you've had.

TB: I was involved in teaching medical students, psychiatric residents, and fellows all through the years, supervising undergraduate and postgraduate students, and mentoring some of those interested in pursuing a career in our field. It was rewarding to see that *Psychopharmacology for Everyday Practice*, a book I published with Marc Hollender, was translated into Dutch and Japanese, and was used in teaching in those countries. And it has been most rewarding to see some of the Fellows trained in our WHO program, becoming professors and heads of departments in their home countries.

WB: Your teaching had an international impact. Did you have administrative responsibilities?

TB: My first major administrative responsibility was directing McGill's Division of Psychopharmacology. The Division disintegrated shortly after I moved to Vanderbilt. And in the 1990s, I became President and Chairman of the Board of Directors of a company with my former associates that for all practical purposes died before it was born. It was probably unrealistic to form a company that was dependent on industrial support, which was trying to narrow the indications of drugs. So, I would say, I failed as an administrator.

WB: You always had an open mind, contrary to some people. You published extensively throughout the years. How many papers did you publish?

TB: Over seven hundred papers, including journal articles and book chapters.

WB: What was your last publication?

TB: "The Role of Serendipity in Drug Discovery." It reviews the serendipitous discovery of many of the drugs used in psychiatry.

WB: Where was it published?

TB: In *Dialogue*, a journal published by Servier, a French drug company. I was very pleased to learn from Don Kline that he found it useful in preparing for his Oakley Ray history lecture this year.

WB: Were you involved in editing journals?

TB: I was co-editor with Fritz Freyhan and Pierre Pichot of the *International Journal of Pharmacopsychiatry*, and also of the series, *Modern Problems of Pharmacopsychiatry*.

WB: How many books have you written?

TB: Twenty three and edited twenty seven.

WB: So fifty altogether?

TB: Many of my edited books are collections of our studies with the same drug, e.g. trimipramine, trazodone, or drugs form the same family, e.g., butyrophenones, thioxanthenes. I used drug studies to generate information for a continuous re-evaluation of psychiatric concepts and many of my monographs are based on this continuous re-evaluation. *Schizophrenia, A Psychopharmacological Approach*, was followed by *Recent Advances in the Biology of Schizophrenia*; *Depression and the Tricyclic Antidepressants* was followed by the *Psychopharmacology of Depression*; and *Psychopharmacology in the Aged* was followed by *Cognitive Decline in the Aged*. My last monograph, *Classification of Psychoses*, was co-authored by Ronaldo Ucha Udabe, who was, as I said before, one of my former WHO Fellows. He also co-edited with me, *The Neurotransmitter Era in Neuropsychopharmacology*, published in 2006.

WB: That's very impressive. Can you say something about your family?

TB: I got married the day President Kennedy was assassinated. My wife is many generations Canadian. She is a graduate of the University of Western Ontario. She was a housewife until our son left for college, but after we moved to Toronto, she became an actress. Our son majored in history and political science, then, after he got his Masters in European Community Law, he became a documentary filmmaker. He lives nearby in Toronto. We are a close knit family.

WB: What are your current activities?

TB: I am editing ACNP's ten volume oral history series on the first fifty years in the development of neuropsychopharmacology, which, in itself, is a full time job. It will complement CINP's four volume history series I co-edited with David Healy and Edward Shorter, in which the same period was reviewed in autobiographical accounts. These two series should provide authentic, firsthand information on the birth and early development of neuropsychopharmacology. I am also serving on an independent commission of inquiry, set up by the Canadian University Teachers Association, to find out what led to the seizure of the research files of a group of distinguished researchers by their Institute's ethics committee. We hope that by getting to the roots of the problem we would be able to make recommendations that could help prevent such a drastic measure being taken again. Finally, I have started to develop a new methodology I refer to as "nosologic homotyping" for identifying empirically derived pharmacologically homogeneous psychiatric populations.

Nosologic homotypes are identical in psychopathologic symptoms, not in the content of symptoms of course, and are assigned the same position in the “nosologic matrix,” based on three nosologic organizing principles, which are totality, temporality, and polarity. They are more homogenous in mental pathology and provide more suitable end-points for biological research than DSM-IV or ICD-10 diagnoses.

WB: I want to ask you one more question and that is about the future. What do you think is going to happen, both in terms of your contributions or in terms of the field in the future?

TB: I believe we will identify pharmacologically more homogeneous populations in the next decades that will break the impasse of developing clinically more selective drugs, which in turn would open the path for molecular genetic research in psychiatry. I also believe that the identification of these populations will be based on research in psychopathology and psychiatric nosology and not in research on biochemistry, neurophysiology, endocrinology, or molecular genetics.

WB: Is there anything else you would like to add?

TB: I would like to add that while clinical research in conditioning has been dormant, basic research in conditioning continued and by the dawn of the 21st century, the structural and functional foundation of classical and operant conditioning have been discovered in the brain. So, if it would be verified that the abnormal connections between and across mental structures, the structural basis of psychopathology, are CR connections, as some structural psychopathologists suggest, I could imagine, by letting my fantasy fly, that CR variables would provide a “code,” something like the genetic code, that would define psychiatric disorders. The idea of course is not new. Its roots are in the research of Griesinger and Pavlov.

WB: Did I miss anything?

TB: I think we covered everything important and even some of my fantasies.

WB: I see you as being there from the very beginning, continuously active in research, writing a huge number of papers and books, and communicating across the different areas of our field. We talked about Heinz Lehmann, one of your mentors, being a giant. I think you also are a giant in this field. I really enjoyed talking with you and having a candid interview.

TB: Thank you. I enjoyed talking with you too.

2. ARVID CARLSSON

WB: I have the honor today of interviewing Dr. Arvid Carlsson* from Gothenburg, Sweden, and I wonder if you'd start by telling us what your current position is and your title.

AC: I am Emeritus Professor of Pharmacology at the University of Gothenburg, Sweden.

WB: OK. Can you tell me what kind of training you have?

AC: I am a medical doctor, so I had my original training at the University of Lund, which is in the "deep south" of Sweden. My training in medicine and the work on my thesis in pharmacology were done in parallel and both were completed in 1951.

WB: What was the thesis on?

AC: That was on something entirely different from what we are going to talk about. It was on calcium metabolism. At that time radioactive isotopes had become commercially available and this, of course, opened up tremendous opportunities for studying metabolism of various compounds, including calcium. So, that was what my thesis was about.

WB: How did you first become interested in psychopharmacology?

AC: Shortly after defending my thesis, I applied for an associate professorship in pharmacology. We were two, who competed, and I didn't get it. The panel examining us let me understand that calcium metabolism wasn't really the thing that pharmacologists should be doing. So I went to an elder friend of mine, Dr. Sune Bergström, professor of biochemistry at the university and asked him whether he could find a laboratory in the US where they were doing some really fine modern work in biochemical pharmacology. He wrote to a friend of his at the NIH and it ended up with a letter of invitation from Dr. Bernard B. Brodie at the Laboratory of Chemical Pharmacology at the NIH.

WB: Who were your colleagues when you were there?

AC: Sidney Udenfriend, for example, was there, a very well-known name. The person who was my immediate mentor was Dr. Parkhurst A. Shore and I must say that laboratory was kind of a

*Arvid Carlsson was born in Uppsala, Sweden, on January 25, 1923. He was initially trained in medicine and pharmacology at University of Lund and received the M.D. and Ph.D. degrees in 1951. He then became a professor at the University of Lund. In 1959, he became a professor at the University of Gothenburg. He is best known for his work with the neurotransmitter dopamine and its effects in Parkinson's disease. For his work on dopamine, Carlsson was awarded the Nobel Prize in Physiology or Medicine in 2000, along with co-recipients Eric Kandel and Paul Greengard. He was interviewed in Las Croabas, Puerto Rico, December 12, 1998.

Mecca of modern pharmacology. Brodie, together with Udenfriend and a doctor named Bowman, had developed an instrument that turned out to be extremely important because it was a very sensitive tool for measuring levels of both drugs and endogenous compounds in body tissues and fluids. It was called a spectrophotofluorometer. That was the instrument by which one could, for the first time, measure very low levels of various endogenous compounds, such as neurotransmitters. That was a breakthrough.

WB: My impression was that the Laboratory of Chemical Pharmacology was probably the hottest laboratory in the world, maybe, at that time, in terms of the people there.

AC: That's true. There was a stream of visitors all the time from all parts of the world.

WB: Wasn't Fridolin Sulser there for a while?

AC: Fridolin came later. One person, who came at the time I was there, visiting frequently, was Nathan Kline, and he picked up some things there. This was in 1955, by the way. Shore and Brodie had shortly after my arrival discovered that reserpine, an antipsychotic and antihypertensive drug used in those days, caused a virtually complete depletion of serotonin in tissues, including the brain. There was another person, Alfred Pletscher, who came from Basel, from Hoffman-LaRoche. He brought iproniazid, which was the first monoamine oxidase inhibitor, and the interaction between reserpine and iproniazid was so intriguing to Nathan Kline that it ended up with Nathan Kline actually demonstrating the therapeutic action of iproniazid in depressed people, another important discovery.

WB: He got the Lasker Award for that.

AC: Twice, he got it twice, for discovering the antipsychotic action of reserpine and the antidepressant effect of iproniazid.

WB: What was the work you were doing when you were in Brodie's lab?

AC: That was on reserpine. I was very lucky, because as I mentioned, only a couple of months before I came, Shore and Brodie had discovered the serotonin-depleting action of reserpine. I was given the opportunity to show, in in-vitro experiments in blood platelets, the action of reserpine on the storage of serotonin.

WB: And, how long were you there in Brodie's lab?

AC: Five months.

WB: OK, and then, you went back and what did you do when you got back?

AC: Actually, when I was there, I asked Brodie, shouldn't we also look at some other compounds besides serotonin to see whether reserpine could act on those and Brodie said, no, he didn't think so. He was so sure serotonin was the most important compound, insofar as psychosis was concerned; he thought it would be a waste of time. So, I thought perhaps I can do that when I get home and I wrote to a friend of mine, an associate professor of histology in Lund, Nils-Åke Hillarp. He had just made the very important discovery that there are organelles in the adrenal medulla that are capable of storing adrenaline and noradrenaline together with ATP. It was very intriguing. And, I thought, maybe reserpine acts on these organelles. That's why I wrote to him, asking if we should look at this and he agreed. Apparently, reserpine acted in a similar manner on organelles in the adrenal medulla, in the noradrenergic nerves and in the serotonin-storing cells.

WB: So, all these monoamines are stored in a similar manner?

AC: Absolutely, all monoamines. Of course, dopamine was not being discussed at that time.

WB: So, take me through your career in terms of the high points of the research. I think that's what we really need to do.

AC: Hillarp and I did these experiments and found that also noradrenaline and adrenaline stores are depleted when you give reserpine. We also found that if you stimulated the adrenergic nerves following reserpine treatments, they didn't respond anymore, so we believed that after the neurotransmitter had gone, the nerves couldn't function any more. This was actually opposite to the hypothesis of Brodie, because he believed that what reserpine does is to cause an ongoing release, so it's more or less the opposite from the point of view of the function of the system. But we were in favor of the depletion hypothesis. Reserpine has a very pronounced behavioral effect; the animals become immobile and are heavily sedated. We felt that perhaps we can reverse this condition by giving norepinephrine or serotonin and then see which one is important. But we couldn't give the amines themselves, because they don't get into the brain; we had to give the precursors, L-DOPA and 5-hydroxytryptophan. We found a most striking effect when we gave L-DOPA. The animals started to wake up within ten minutes following an IV injection and then, behaved like normal animals.

WB: It must have been exciting when you first saw this.

AC: We were just as excited as the animals. It was really dramatic. We were so excited that we very quickly wrote a letter to *Nature*, sending a photograph of the response. They accepted the letter, but they didn't think the photograph was worthwhile. But at that time when we sent it off,

we hadn't yet analyzed the brains. We were sure that there should be a lot of noradrenaline in those brains since the animals responded so nicely, and we were, of course, greatly disappointed when we found there was still no noradrenaline. In order to save our face, we thought, maybe at least, we could look for dopamine in the brain, because that is an intermediate between L-DOPA and noradrenaline. We had to develop a method for measuring dopamine, and then, we found that, sure enough, the response to L-DOPA could be correlated very closely to the formation and accumulation of dopamine in the brain. We also found that dopamine does indeed occur in the brain under normal conditions and not just in those small levels you would assume an intermediate would have. Actually, the levels were a little bit higher than those of noradrenaline. From all these findings, we proposed that dopamine is an agonist in its own right in the brain.

WB: Was that the first time that was proposed?

AC: That was the first time. We were the first to identify dopamine in the brain, in 1958, and to propose a role for it in the brain. And soon afterwards we proposed that parkinsonism could be due to dopamine deficiency and that L-DOPA could have an anti-parkinson effect. We were very excited and went to a meeting shortly after that, Hillarp and I, in London, on Adrenergic Mechanisms. There were all the big shots, with Sir Henry Dale on top, and we reported on these things, but were disappointed that they were not impressed. We got all kinds of questions such as, is it really true these amines could have a function in the brain? They didn't believe so. Marthe Vogt, for example, was very much against it, like many others, and the British pharmacologist Paton referred to some unpublished data indicating that these amines are in the glia and had no importance. We were very disappointed. We thought, now we at least had to prove that these amines do occur in nerves. Hillarp was a very clever histochemist, so he developed a method that enabled us to see where these amines are located and, indeed, they are in the nerves. They are not in the glia and they had a distribution that was very much the same as in peripheral adrenergic nerves, where it was known already that noradrenaline is a neurotransmitter. That was very important to convince the scientific community that in the brain you have chemical transmission as in the peripheral system and not, as was generally believed, that signaling between the nerves in neurons in the brain was electrical only. Our findings triggered the concept of chemical transmission in the central nervous system.

WB: So, that opened up a whole conceptual field.

AC: Yes, absolutely. Before that, the kinds of questions that were dealt with in psychopharmacology and CNS physiology had to do with carbohydrate metabolism and the like. If you go into the 1970s, if you look at journals then, nearly all research in the central nervous system is centered around neurotransmitters, so that was a revolution in neuroscience.

WB: Now, take this into the pharmacology, in terms of the drugs.

AC: Brodie's interest in reserpine was due to the discovery a few years earlier that reserpine and chlorpromazine have such a dramatic effect in psychosis and schizophrenia. The discoveries just mentioned opened up entirely new aspects of the mode of action of antipsychotic drugs and, as a consequence, new hypotheses about the pathogenesis of schizophrenia, for example, the dopamine hypothesis. While reserpine causes depletion of monoamines, the other major antipsychotic drugs, the ones that are now in general use, such as chlorpromazine, did not cause depletion of the amines, so we wondered how they could act. We discovered in 1963, for the first time, an effect of chlorpromazine, haloperidol and similar agents on dopamine and noradrenaline metabolism that turned out to be in the direction of stimulation. This was opposite, in terms of function, to what reserpine did. On the basis of that and a number of other observations at that time, we proposed that chlorpromazine and haloperidol block dopamine receptors, rather than depleting the neurotransmitter. The outcome would be similar whether you give reserpine to cause depletion of the catecholamines or give chlorpromazine to cause blockade of dopamine and noradrenaline receptors. Further along, when our studies continued and others came in, it turned out that dopamine seemed to be more important than noradrenaline, even if we still could not exclude a contribution by noradrenaline.

WB: Wasn't this one of the major pillars and pioneering sort of framework upon which people started to think about mechanisms of action of antipsychotics?

AC: Yes, absolutely, and the antidepressants were discussed in similar terms.

WB: But, this was another first.

AC: That's right; the antidepressants came in somewhat later. First came iproniazid, which was a monoamine oxidase inhibitor that Nathan Kline had found was an antidepressant, and then came imipramine and it was in the early 1960s that the first observations on an effect of imipramine on noradrenaline uptake was reported.

WB: And, some of that was done in Brodie's lab, too, wasn't it?

AC: The first observations concerning uptake of norepinephrine in the brain were in Brodie's lab and he was very much interested in that and had the idea imipramine didn't act on its own but was a pro-drug. They suggested that it was desipramine that was active. That was based on some behavioral experiments done in his lab.

WB: OK, then what happened in your career? What were the other high points?

AC: We worked for a long time to pursue our catecholamine work, but an entirely different thing came up a little later and went back to serotonin. What we found was that imipramine did not only block the re-uptake of noradrenaline but also serotonin. We went through quite a long series of tricyclic antidepressants and found that practically all of them had effects on both the uptake of noradrenaline and serotonin, but there were differences. There was one compound, chlorimipramine, that was particularly strong in its action on serotonin, so we were very excited about that and I still remember I went down to Geigy in Basel and told them this is a compound you should bring to the clinic. They didn't believe much in it. They had another candidate, but, fortunately, the other candidate turned out to have a problem in toxicity, so they did develop chlorimipramine and it turned out to have a very interesting pharmacological profile, different, for example, from imipramine.

WB: Was it effective in depression and obsessive compulsive disorder (OCD)?

AC: That's right. That was the most important part with chlorimipramine, the whole area of anxiety, panic disorder and OCD. Regarding OCD, that was the first time one had a drug that really could do anything in this disorder. We started to look at other types of molecules to see whether they could have an effect on the uptake of serotonin and came across a series of antihistaminic compounds; one of them was brompheniramine. That compound turned out to be especially powerful. Like many other antihistamines it acted both on serotonin and noradrenaline re-uptake, but brompheniramine was relatively strong on serotonin. I collaborated with a very clever Swiss organic chemist, who was working in Sweden at the Astra Company and, together, we modified brompheniramine on two sites and, as a result, we came to zimelidine. Zimelidine was the first selective serotonin reuptake inhibitor (SSRI). In clinical testing it was found to be an antidepressant and, later on, also found to be a powerful drug in panic disorders. I am not sure if they collected data also on OCD but I think they did. Unfortunately, zimelidine turned out to have a rare but serious side effect, so the Astra Company decided to withdraw the compound. In contrast to the tricyclic antidepressants, zimelidine didn't exert any anticholinergic action or cardiotoxicity.

WB: So, zimelidine was really the first in the family of the SSRI's?

AC: Absolutely.

WB: It was the prototype.

AC: It was the prototype for Prozac, for example. At Eli Lilly, they started to work on Prozac at about the time we submitted the first patent for zimelidine.

WB: OK, what happened next?

AC: What I would like to talk about is our interest in neurocircuitries. We started out from dopamine as a platform to see how dopamine interacts with other neurotransmitters. In that context we became interested in glutamate. We got into this at a very early stage at a little group of which both of us are members, which has a meeting in the Caribbean every year. Actually, at that time, I remember the NMDA receptor had just been characterized and that phencyclidine had been found by Lodge and his colleagues to block the NMDA receptor. At one of these meetings in the Caribbean, I learned from you that phencyclidine is even more powerful than the amphetamines in mimicking schizophrenia, especially with respect to the negative symptoms. On that basis, we developed a scheme which started to evolve. According to this, glutamate and dopamine are powerful controlling agents in the basal ganglia in the sense that they are antagonizing each other. The basal ganglia, in turn, control the thalamus, which we thought could work as a filter, and this could be important in the pathogenesis of psychosis. If this filter opens up too much, the sensory input will overload the cerebral cortex and that might lead to psychosis. That was the concept of a circuitry from which we started out. Later on, when I started to test it pharmacologically, together with Maria Carlsson, we found much support for it, but also that it was more complicated. We had evidence that glutamate and dopamine can, under certain conditions, act in concert so there are pathways where they oppose each other and other pathways where they operate together.

WB: Which drugs did you study?

AC: There is no doubt that it was reserpine that was the starting point for our research and it's interesting that we have been using it ever since. Many people felt this is an obsolete drug, even in research, but we don't agree. I think reserpine is the drug of choice, if you really want to cause a depletion of the monoaminergic system and monoaminergic pathways and be sure you can disregard the presynaptic monoaminergic mechanisms. There is no other way, really, of being absolutely sure than to give reserpine and add inhibitors of the synthesis of these amines.

WB: You've listed a number of the famous people who've had impacts on your career. Are there others that should be mentioned?

AC: Well, I did mention the most important ones: Brodie, Hillarp and Corrody. I've had, of course, lots of collaborators who have been very important to me.

WB: What do you think was your most significant contribution?

AC: I really don't know. I think I have been so excited all the way along by the various things that showed up.

WB: All right. How did you stay in the field and do science, rather than taking administrative jobs, which I'm sure were offered to you on many occasions?

AC: I was very energetic in that context. I insisted that my secretary should do the work that I was supposed to do, so whenever one of those brown envelopes came, I gave it to her and I'd say I couldn't care less about it; you take care of it. So, I stayed out of administration. I was on a couple of faculty committees but I didn't please the other members, so I got out of them rather soon.

WB: Are you happy with the way things turned out for you?

AC: Yes, I must say I have been very lucky in many respects. I was lucky at the very outset to get to this fabulous laboratory, and then, to meet such wonderful people, like those I have mentioned already. So, yes, I have been fortunate and I am very pleased.

WB: Where do you see this field going in the next 5 or 10 years, and what new drugs might be developed? What illnesses might be treated?

AC: I have the feeling that in the area of depression, affective disorders and anxiety disorders, there have been really significant advances during the last few decades; in contrast, in the area of psychosis, where progress has been less striking. So, I think that the most likely area where we are going to see some real breakthroughs is in the area of psychosis and schizophrenia. And, we see some signs of that already. I think that clozapine has opened up very interesting new avenues and points to the importance of neurotransmitters other than dopamine. Especially, serotonin is coming into the picture of psychosis in a very interesting manner. This is one avenue where some progress is now underway with new drugs that are clozapine-like, yet not toxic like clozapine. They seem to offer promise, even though I think that it's not going to be a very great step, but still significant in comparison to the drugs available now. Then, I think other new principles of

different kinds will be related to glutamate. Furthermore, the newly discovered receptor subtypes have to be considered. We have the area of partial agonists that I believe are very promising.

WB: You've done a fair amount of work on partial dopamine receptor agonists such as (-)-3PPP.

AC: That's one of my favorite areas, actually. And a clean 5HT₂ receptor antagonist; one such compound is actually now being tested in the clinic in schizophrenia. So, there are at least three or four areas that offer great promise. Within the next 5 or 10 years, there has to be a breakthrough. I consider it almost unthinkable that all these four should be failures.

WB: What are the four again?

AC: It will be the mixed kind that clozapine offers with drugs such as olanzapine. That is number one. That is closest. We are almost there. Then, the pure 5HT₂ antagonists, this is probably somewhat related to clozapine, but still different. We have the partial dopamine receptor agonists and, finally, we have the whole new area of glutamates. These receptors, for example, the NMDA receptor, is a very complicated receptor with many different binding sites that offers enormous possibilities. I mean, a lot remains to be done to characterize this receptor with its subunits and possible subtypes. You have one binding site where glutamate comes in. You have another one where glycine sits. There is a lot of effort now ongoing in the area of the glycine site. If we look a little bit more ahead, maybe, 10 years from now, I wouldn't be surprised if the glutamate area is going to be very important in the field of psychosis.

WB: Are there any other issues that we should have covered?

AC: I might like to talk a little bit about some of our post mortem studies, which I think are interesting. What we did was to examine various monoaminergic indices, in other words, levels of dopamine, noradrenaline, serotonin and their metabolites and precursors in post mortem brains, in schizophrenics, as well as in controls. And, we did first conventional statistics on the measurements we had done and didn't find much. Then came a young man, who was very talented in multivariate analysis, who fed all the data into a computer and used some clever programs; out came patterns in which all these variables were viewed at one time, a multidimensional body that could be projected to a two dimensional picture to see whether there were any clusters. What showed up was one area where you had all the controls and two others where you had the schizophrenics that were quite different from each other. One of them turned out to be paranoid and the other one non-paranoid schizophrenics. So, from that starting point, I very strongly believe in the methodology of multivariate analysis and we're using it, not only on post mortem material,

but also in our preclinical work. For example, I had the privilege of having in my group a number of clever organic chemists. They are synthesizing compounds for us and if you wish to characterize the pharmacological profile of the various compounds on behavior or the chemistry of the brain, then, multivariate analysis is extremely powerful and I think should be used a lot more.

WB: Any other areas?

AC: I think we'll stop now.

WB: OK. Let me just say that Dr. Arvid Carlsson is, in my view, one of the pioneers in the field of neuropsychopharmacology. He was recently selected for the Japan Prize among all neuroscientists and individuals in psychology and psychiatry and I consider that a great honor, well deserved, and a timely recognition of his pioneering contributions to the field of neuropsychopharmacology and to neuroscience.

AC: Thank you.

3. JOSEPH T. COYLE

WB: I'm William Bunney and I am interviewing Joe Coyle*. It is December 22, 2007 and this is the 46th meeting of the ACNP in Boca Raton, Florida. First question is: where were you born?

JC: I was born in Chicago, Illinois.

WB: And, tell me a little bit about your education.

JC: Okay, my father was a physician in Chicago and my mother was a nurse. I had two older sisters and grew up on the south side of Chicago. I went to a Jesuit high school, where I studied Latin, Greek and French and went off to Holy Cross College in Worcester, Massachusetts, which was a Jesuit college.

WB: Do you know Hebrew?

JC: Actually, my roommate was taking Hebrew and I ended up being a French and Philosophy major. I did my required science courses mostly in the summer school and had the good fortune to spend my junior year living in Paris, which was really a life-altering event.

WB: How was that?

JC: Well, I grew up in parochial schools with a big P and a small p and so, at Holy Cross, we went to Mass every morning and we had to have lights out by eleven o'clock. Then, suddenly, I was dropped into Paris, where there were no rules and it was a very different culture. It was a time when students were starting to organize.

WB: Now, where was this in your education?

JC: This is 1963-64.

WB: And, this was College?

JC: College. I was there in 1963, when Kennedy was assassinated, which was very striking, because the city, the Nation, France just shut down for his mourning. And, you could really see how much impact he had on the world. So anyway, I applied to medical school and I remember I

* Joseph T. Coyle was born in Chicago, Illinois, on January 25, 1943. He received his M.D. degree from Johns Hopkins School of Medicine in 1969, where he also completed his residency in Psychiatry. He completed an internship in pediatrics, a residency in psychiatry, and a fellowship with the Nobel laureate Julius Axelrod, PhD in the Laboratory of Clinical Science, National Institute of Mental Health in Bethesda Maryland. He joined the Hopkins faculty in 1975 and was named the Distinguished Service Professor of Child Psychiatry in 1985. Coyle is the Eben S. Draper Chair of Psychiatry and Neuroscience at Harvard Medical School and Chief Scientific Officer at McLean Hospital. He was interviewed in Boca Raton, Florida, December 11, 2007.

was interviewed at Hopkins and they asked me if I had done any research. And, I said, oh yes, I did a lot of research on Samuel Beckett. But, anyway, I ultimately was accepted at Hopkins and I went there with the plan of being a psychiatrist. I had read a lot of Freud and Lacan and was very interested in psychoanalytic thought and existential philosophy. In my sophomore year, I was taking a pharmacology course and there was this psychiatric resident named Sol Snyder, who was teaching a new section in the course called psychopharmacology.

WB: Now we are at Hopkins?

JC: Yes, we are at Hopkins and he was a faculty member in the Department of Pharmacology and he was, I think, a second year resident in psychiatry. The lectures were just really exciting. It was a whole new way of thinking about the brain and behavior, LSD, stimulants, antipsychotics, antidepressants and he would sit on a tall stool with a big jug of water and would give his lectures. And we all fantasized that it was a jug of martinis, of course.

WB: What was the year of this?

JC: So this would be 1967. I went to see him and said, you know, I'd really like to spend some time doing research in your laboratory. Of course, he was interested in as many hands as he could get and he said, sure. So, the first quarter in my junior year was a free quarter. He did something, I think, very, very special. He really allowed you to do your own research, design experiments. So, within two weeks, I was immersed in this whole process of discovery. And, I did bring one thing to the lab, because I had a project in biochemistry and I had read about these things called synaptosomes. Sol was studying neurotransmitter uptake using a McIlwain tissue chopper to chop up the tissues. The problem with that is that the tissue settles out of solution in the pipette. I suggested that we work with synaptosome. We did and, of course, it's like milk and you'd get very accurate pipette results. So, that was my introduction to research. And during the period of time that I worked in the laboratory, I was able to identify that the dopamine transporter was different from the norepinephrine transporter and that was published in *Science*.

WB: Was that your first paper?

JC: That was my second paper.

WB: What was your first paper?

JC: My first paper was in the *Journal of Pharmacology and Experimental Therapeutics* on characterizing norepinephrine uptake in the synaptosome preparation.

WB: You started off with a bang.

JC: So, in my junior year, I had an elective or free quarter when I worked in Sol's laboratory and then, I did my mandatory medical, surgical and pediatric rotations. In senior year, you were supposed to redo surgery and medicine rotations. That seemed kind of silly and I wanted to do more research and so I was a special case that they put forward to the Dean to see if I could take more elective time. Ultimately, that resulted in the rules changing at Hopkins, allowing more elective time for the medical students. I graduated and did a pediatric internship and I was interested in ultimately doing child psychiatry.

WB: And where was that?

JC: At Hopkins.

WB: At Hopkins, too, yes.

JC: Right. I interviewed for positions down at NIH and I should point out that medical school was a bit of a struggle for me, especially the first two years, because I had such a light science background. When I went to interview for NIH, I interviewed with Floyd Bloom, Erminio Costa, and Julie Axelrod. I will never forget my interview with Erminio Costa. I go in and sit down and he looks at my transcript. I'd never seen my transcript. Hopkins never told us what our grades were. He looks at my transcript and says, "What are you doing here?" And I said, "What do you mean?" And he said, "These grades, these grades are terrible!" I replied, "Well, you invited me." Anyway, I had the good fortune of being accepted into Julie's lab and, so, I went right after my internship and spent three years in his laboratory. The first year was 1970. It was the year that he won the Nobel Prize, which was very exciting.

WB: So, there was no residency there?

JC: No. Well, what happened was I was planning to do a residency, but Julie had a slot open and said, I can't guarantee I'll have a slot in three years. Since I watch news at night and I wasn't interested in going over to Vietnam, I said, "Okay let's do it." So, I spent three years in his laboratory and it was just great; you know, every morning when you wake up, you are all charged up to go to the lab.

WB: Can't wait to go to work.

JC: Julie was an incredible mentor and he pretty much let us do what we wanted to do as long as it was within the broad theme of the laboratory. I wanted to study the development of the catecholaminergic system in the brain; there was nothing published at the time on neurotransmitter

development at all. And, that was fine with him. Ultimately, several of the papers I published, he said, I really didn't have much to do with that, so you don't have to put my name on the paper. That was the kind of person he was. His desk was right next to the scale and everybody would have to weigh out their reagents every day. So, everybody would go by and there would be Julie reading papers and every once in a while he would say, come over here and tell me what you're doing. And, then, you'd review the data with him and he'd make suggestions. So, it was a very light handed type of supervision. But he did other things that I think were extremely important. He'd obviously get a lot of papers to review. He'd give these papers to the post docs and then he'd go over our reviews and make constructive criticism. Pretty soon we'd be getting the request directly from the journal, so he was creating some visibility for us. Sometimes he'd not be able to give a lecture and he'd send one of us in his place and, so, he really taught you, not only how to think about science, but how to be a scientist and how to develop yourself as a scientist. So, that was an extraordinary experience.

WB: How did you view his thought processes, his scientific thought processes?

JC: Well, you know...

WB: Nobel Laureates often have a unique way of viewing the world. How would you characterize his?

JC: Well, one of the things he taught us was that in ninety nine percent of the experiments that you do, you know what the results going to be; and that the one percent, when you get completely unexpected results that's the most important one. You need to redo it and make sure, in fact, that that is the outcome, and then, there is a sort of head scratching thing. And that's where you can get some very interesting insights, because then you're going out in a way that other people aren't thinking about. He would always say, "Be there firstest with the mostest."

WB: Which meant what?

JC: Well, it meant get into an area that isn't crowded, and then, really flesh it out. I found that very helpful. I've tended to work in areas that aren't very heavily populated; sometimes you can get burned with it because you can be too far ahead of the curve. For example, one of the very hot animal models now for schizophrenia is the methylazoxymethanolacetate or MAM lesion model. We published on the MAM lesion in *Science* thirty years ago and couldn't get an NIH grant funded for it in schizophrenia, because everybody believed back then that schizophrenia was a functional

disorder and didn't result in structural changes in the brain. I went after that because nobody was doing it. It seemed important to me and that's the way Julie would do it.

WB: So, key mentors that you had were Sol and Julie. Were there other people, other key mentors?

JC: Well, sort of an academic mentor was Guy McKahn, who was the head of Neurology at Hopkins. He was out of my specialty, but he knew about the brain and he was very helpful in thinking about making academic decisions.

WB: So, you've talked about your first project, but has there been a central theme throughout your research?

JC: Well, another thing Julie would say is that you follow the result; that's what guides you. And, so, I got into glutamate 32 years ago and had the *Nature* paper with Robbie Schwarcz, my first post doc, when we injected kainic acid into the striatum and reproduced the pathology of Huntington's disease. That suggested to me that, at a time when many scientists didn't believe that glutamate was neurotransmitter, that this could be a very important transmitter. So, glutamate has been a theme of my life for the last thirty years, one way or another. I did a lot on neurodegeneration. I've been working on glutamate and schizophrenia for over a decade, so that's been a major interest. I did a lot of developmental work from the 1970s to probably the mid-1980s, and then moved on from that.

WB: Are there technological developments that came along with this?

JC: Well, one of the things I learned from Sol is to keep it real simple; find a simple assay and really milk it for what you can get. And, I'm not saying that in a cynical way; it can be very efficient. So, one of the exciting things about science is that it's not like being on the Ford assembly line. You're not doing the same thing every day. What I've enjoyed about my career is that we've done a lot of different things. I mean, I started out classical enzymology and I got to immunocytochemistry; and ligand binding and then molecular biology came along. We are kind of like sharks; if we don't keep moving, we are going to die. And, for me, that's been a challenge. It's been exciting to find new ways of thinking about brain.

WB: Almost the renaissance. Okay, financial support?

JC: We've lived through the generosity of our citizens, through the funding to NIH; although, there have occasionally been some lean times. I've been continuously funded since I started my career and feel very lucky to be funded now. I know how difficult it is for many good people to

get grants. I think we live in very perilous times right now for science. NIH and NARSAD have been generous over the years.

WB: And what would you say your major findings were?

JC: Major findings? Well, a couple of different things. When I was doing developmental research, we were able to show that aminergic systems are among the earliest to be formed in the brain. I think that now it's plain and clear that these systems play a major role in regulating brain development. We sort of predicted that, but we didn't have the tools to really answer that question in the 1970s. Second major finding was the kainic acid lesion and people are still thinking about "excitotoxicity" in Huntington's disease. And, you know, we predicted back then that glutamate might be important for neurodegenerative processes.

WB: Were you one of the first to say that?

JC: Well, I have to give some credit to John Olney. He was the first to really define "excitotoxicity." But all his work had been done by administering glutamate in the periphery; and in the areas of the brain where the blood-brain barrier was deficient, would there be neural degeneration? Where we made, I think a strategic advance, was to take potent glutamate receptor agonists and inject them so you could make predictable lesions in specific regions of the brain. And, we used that technique to lesion the nucleus basalis and showed that this reproduced the cholinergic deficits of Alzheimer's disease.

WB: Have you made that landmark finding of glutamate neurotoxicity?

JC: Well, we did. I looked at ISI and we are pretty heavily cited; we are up to forty thousand citations so far.

WB: Well, that's impressive.

JC: Until memantin (Namenda) came along, the only treatments available for Alzheimer's disease were directed at reversing the cholinergic deficits and, though they may not be the greatest, they certainly help some people.

WB: Right, right.

JC: And then, more recently, we've been working on this hypothesis of NMDA receptor hypofunction as being the proximate cause of the pathophysiology of schizophrenia and I think at this meeting it's very evident that we now have a pathologic circuit in schizophrenia that makes a good deal of sense. We actually predicted that in a paper we put out in 1996. It was the working hypothesis for our research program on schizophrenia. We applied four times for a NIMH center

grant on schizophrenia and got it on the fourth time. Again, we were a little bit ahead of the time then, but it certainly has worked out quite nicely, I think. When I was running this schizophrenia clinic at Hopkins, Sol came up with the dopamine hypothesis, extending Arvid Carlsson's work. We were doing dopamine radioreceptor assays to measure neuroleptics in blood to optimize treatment. At the end of the day, it was very discouraging because we thought we knew what was going on with the disorder, but those patients were still profoundly disabled. Now, it is extremely gratifying that we may be able to get a handle on this very disabling disorder.

WB: So, what are the targets you see now for future drug developments?

JC: Already we have this very wondrous finding by Lilly that their mGluR2/3 agonist tracks right on with olanzapine in terms of antipsychotic efficacy. It would be acting at the downstream disinhibited glutamergic pyramidal neurons that are driving subcortical dopamine release. As David Lewis has pointed out, the hypofunction of NMDA receptors is specifically on the GABAergic interneuron, so they end up being hypofunctional. As we've shown at this meeting, when you knock out serine-racemase so there's no D-serine, which reduces NMDA receptor function, you get the reduction in GAD 67 and the reduction in parvalbumin that is the neuropathologic signature of schizophrenia. So, as David has pointed out, another target would be the postsynaptic GABA-A receptors. Certainly, a third target would be more proximal, which would be anything that would enhance NMDA receptor function via the glycine modulatory site, like glycine uptake inhibitors. We actually published, ten years ago, the first report on glycine uptake inhibitors enhancing LTP and NMDA receptor function. I know a number of companies are looking at that site now. And, we've also used D-serine, itself, which is a potential treatment.

WB: Who are some of the other people in the field that are working in the area that you are working in?

JC: Well, there are a number of people and, of course, I think we all like to point out that I did this, or I did that, but it's really based on findings of many other people. David Lewis and Francine Benes, in their post mortem neural chemical studies, I think, have been extremely important. I mean, back ten years ago, you really did feel like the blind people and the elephant, because there was a finding here and a finding there but it was not coherent. Now these findings on the GABAergic interneurons have been highly replicated, so I think their contributions have been extremely important.

WB: Are there others?

JC: You.

WB: Okay, others?

JC: Well, you know, some of the imaging work, like Marc Laruelle's, has been very important. What has also helped us immensely are the results from the genetic studies that are coming out, that several putative risk genes are clearly involved in neurotransmission and several of them are within two degrees of separation from the NMDA receptors.

WB: Do you see patients now?

JC: No, I don't. When I became the Chairman at Harvard, my schedule was so chaotic that it was difficult to maintain a practice.

WB: Before that, did you?

JC: Oh yes, when I was Head of Child Psychiatry at Hopkins, I had a substantial group of patients that I followed. They grew up with me, so to speak, kids with serious mental illness, autism. And I would attend two months of the year our inpatient units. I miss that part of my life.

WB: Let's just go through your career, because we sort of skipped around. So you were with Sol and then...

JC: I went to Julie's lab and...

WB: ...when you left Julie's lab?

JC: Julie let me stay a third year, so I spent three years in Julie's lab and, then, I started to look for residencies. Sol had worked out this deal to do residency and be on the faculty in the Department of Pharmacology and, so, there were two places I was looking at, one was MGH with Seymour Kety and the other was Hopkins. At Hopkins, they said I could start on the Pharmacology faculty in my second year of residency and also with my laboratory, and Seymour Kety said, well, we don't do that at Harvard, and I said, well, gee, I'm sorry, and, so, I went to Hopkins. Seymour wouldn't talk to me or recognize me for about fifteen years. Then we got to be good friends.

WB: Were you happy with Hopkins?

JC: Hopkins was just an extraordinary place at that time. Departments weren't barriers. Neuroscience was just taking off. So, I was collaborating with Mark Molliver in Anatomy, Mahlon DeLong in Neurology, Don Price in Neuropathology and it was great fun. It was great fun and we accomplished a lot. So, anyway, I started on the faculty and I got my first grant in my third year of residency. I got the grant; it was for twenty-four thousand dollars. Twenty four thousand dollars

went a long way back then, so I was able to set up my lab. The first person that I hired was Rob Zaczek as a technician. Rob is a dear friend of mine. He's running neuroscience at BMS now. My first post doc was Robbie Schwarcz, who sold his stamp collection to come over and do the post doc. That was a very productive relationship and he's a dear friend. And, then the lab grew, got more grants, had a developmental project going and had the neurodegeneration project going. And also, I had an Alzheimer's project funded; so we were running on 3 ROIs.

WB: How many people in the lab?

JC: Through the 1980s - I left in 1991 - I would say we had over a dozen people. I really didn't believe in professional technicians, so we would get students, who just graduated from college, who were uncertain whether they wanted to go to graduate school or medical school and they'd come work in the lab. We had those, and everyone, except one, either went to graduate school or went to medical school. Some of them are successful scientists now. For example, I ran into Paul Schlesinger recently. He was a technician with me and now he's on the faculty at the Salk Institute.

WB: So, you moved up to become Professor there.

JC: Right. I finished my residency in 1976 and was made a professor in 1980. And, another interesting part was that I didn't do my training in child psychiatry because by the time I got done with my residency my lab was going. Anyway, I looked around and I couldn't see any place that I'd want to go to be trained in child psychiatry. The programs were very much psychoanalytic and there was very little being done in terms of brain development. So, after Leon Eisenberg left as head of child psychiatry at Hopkins, they tried to recruit a number of people without success. Paul McHugh pulled me aside one day and he said, "What do you think about becoming the head of child psychiatry?" I said, "Geez, I hadn't thought of that." I had to go to a conference up in New England. It was in the middle of the airline strike and I took a train. So, I had all the time to think about it. I decided to take the position considering that, maybe we could have a new way of thinking about child psychiatry with our developmental brain research and bought a textbook of child psychiatry and was able to set up a division populated with people that could teach me what I thought I needed to know and teach our residents what they needed to know about child psychiatry.

WB: I never heard that one before.

JC: So, I recruited Randy Blakely. He was getting his PhD in Neuroscience. Randy is doing great stuff on serotonin transporters in autism. I recruited Joe Pivin, and now he is a Professor at UNC and runs their mental retardation center. I got Alan Reiss, and he's Head of Child Psychiatry at

Stanford, doing great research on fragile X in autism. And, I also recruited Paramjit Joshi, who is now the Head of Child Psychiatry at Children's Hospital in DC.

WB: Were these all the people you hired?

JC: Yes.

WB: That's a nice legacy, too.

JC: Yes, I'm proud of that.

WB: Tell me a little bit about your teaching experience.

JC: Well, I thoroughly enjoyed teaching and when I was at Hopkins, I had faculty appointments in Pharmacology, Neuroscience, Psychiatry, Pediatrics and over in the school of Public Health in Toxicology. I would teach in all those programs. So, I taught several of the lecturers in neuropharmacology in the pharmacology course and several lecturers in the neuroscience course, taught the medical students in psychiatry and worked with the residents and taught them. I really did enjoy that.

WB: In 1991, you moved to Harvard. Why did you move?

JC: When I had come in to take over the Division of Child Psychiatry at Hopkins, it had 3 FMG faculty members and no research. And, after eight years, I had built it up, so we had two thirteen-bed in-patient units and we had a faculty of about a dozen. Most of these faculty members were involved in research. We had grown to a several million dollar research budget in the Division. But, then, the Head of the Hopkins Hospital had set up his own HMO. Medicaid was paying the hospital ninety-eight cents on the dollar for our beds and they were paying us five dollars a day to take care of the patients. So, my Division of Child Psychiatry was starting to go into the red, big time. This HMO would refer the patients to the emergency room, where we evaluated them and then, sent them to a little hospital that they had developed in a Victorian house and they wouldn't pay us for the evaluations done in the emergency room. So, I really was getting annoyed and there was no way to solve the budget problem. I talked to the hospital administrator, who responded that if you're a good businessman, you can solve this. He said, "People in surgery are doing fine. What are you complaining about?" And, then, Dan Tosteson, who was the Dean at Harvard, approached me. He approached me once before, to become the head of MGH and McLean Hospital. I went up there and I saw this sort of tower of Babel, which was Harvard Psychiatry, with all these different competing groups. So, he came back to me and said, "Look, I can put together a deal where you'd be the academic head of six of the nine programs." And he got the

hospitals to commit the money to run the academic programs and it was a pretty substantial offer. I figured that if I did it right, then the other three hospitals would join. Indeed, in about eighteen months, the rest of them joined and this was known as a Consolidated Department of Psychiatry. We got a lawyer to look at this structure and it became clear that I could not deal with clinical services, because we controlled over thirty percent of the clinical services in eastern Massachusetts. That was great, because I was not interested in the business of psychiatry. I was interested in the research and the academic components.

WB: Right.

JC: When I got there, there was no grant that transcended any department and I think the total amount of NIH funding was around fifteen million dollars. MGH psychiatry had less than a million dollars worth of grant funding. Over the years, we got center grants, training grants and, after ten years, we went up to around seventy million dollars for the entire research operation in Harvard psychiatry. And, I was able to condense the adult residencies so that we had three adult residencies with one application. These programs were differentiated. By and large, that worked out. There were six child residencies, and we turned them into three training sites with one core curriculum. The child residencies then became, I think, fairly competitive. So, I was pretty satisfied.

WB: This was your PhD in Administration that you got the same way you did your child psychiatry. It sounds like you transformed the whole place, in terms of academics.

JC: Right, and, then, two things happened. Dean Tosteson, I think in about 1996, had gotten together the heads of the hospitals and said, look, we've got to do something; this managed care is going to come in and it's going to be disastrous if we don't work together. His idea was that Harvard Medical School should take academic ownership of the clinical departments and as usual, psychiatry should be was one of the first experiments. Then, he woke up one morning and read in the Boston Globe that Massachusetts General Hospital and the Brigham Woman's were merging to form this entity, called Partners. I think that was a very difficult thing for him and he had also developed Parkinson's disease. So, he stepped down. The new Dean, who came in, I think was really much more interested in having Harvard Medical School work like it did before, where the Hospitals took the responsibility for the Clinical Departments. So, I had a ten-year commitment and I got done with it and I said, I'm going back to the lab and that was a good decision.

WB: Just to backtrack for a minute, do you remember your first presentation?

JC: Yes, I do remember my first presentation. Neuroscience started in 1970, and back then, the really big meeting for people like me was the American Society for Pharmacology and Experimental Therapeutics. My first presentation was in Atlantic City at the ASPET meeting and it was the last talk on the last day of the meeting and I'll never forget that. It was in a room with about three thousand empty chairs, a projectionist and me.

WB: Really?

JC: Yes.

WB: Okay, what are your most important contributions to the field?

JC: Oh.

WB: You can name a couple.

JC: Well, I think certainly one was the whole excitotoxic story in terms of defining true glutamate receptors and their sub-types. I would say that would be one. I would say a second one, working out this pathologic circuit in schizophrenia, I see that was important. And the third, I guess, would be the cholinergic deficits in Alzheimer's disease. We didn't discover them. Those were discovered in post-mortem studies, but what we were able to do was to work out the anatomy of the cholinergic deficits and that allowed animal models to be developed. And, the last thing, I would say, is the trainees. I mean, I've really been blessed with extraordinary students and post docs and they carry on the legacy. I'm proud of Randy Blakely, who won the Efron award. So he's third generation: Sol, me and, then, Randy. So many others whom I've trained in the lab have gone on to do really good things in science and in medicine.

WB: How many publications you have, ballpark?

JC: It's over five hundred.

WB: Five hundred. And books?

JC: I think it's seven or eight.

WB: Seven or eight books, are these edited or written?

JC: These are edited.

WB: Honors and awards?

JC: I won the John Jacob Abel Award from ASPET, which was, in my mind, a great honor. I won the A.E. Bennett Research Award from the Society of Biological Psychiatry and the Foundation Fund Award from the APA for research. I was elected Fellow of the American

Academy of Arts and Sciences, a Member of the Institute of Medicine and a Fellow of the American Association for the Advancement of Science.

WB: Why don't you comment on what you do in editing journals?

JC: In 2001, Cathy DeAngelis, the editor of *JAMA*, approached me to take over from Jack Barchas as the Editor of the Archives of General Psychiatry. I've been on the editorial boards for a number of scientific journals. The Archives has always been the lead journal in the field, as far as I was concerned, and Danny Freedman was the Editor for a very long time. Danny was a kind of a mentor to me. I had been on NIH study sections with him, and he was just a really neat guy. I was on the editorial board with him. As someone who is probably associated more with basic neuroscience than clinical neuroscience, it seemed to me that Psychiatry was moving into a new realm in terms of understanding psychiatric illness and, so, I was very intrigued about the opportunity to become the editor of the Archives, both in terms of its traditions and in terms of where I think the science may be taking us.

WB: Roles in the ACNP?

JC: I've been on council and I served as a President in 2001. I served on a number of committees; most recently, the Publication Committee with Sam Enna and I think we've been able to make some important changes in terms of the Journal. Hopefully, we will be able to develop a much more robust website and moving from *Generations of Progress* to the new *Annual Review of Neuropsychopharmacology*.

WB: Was that your initiative?

JC: Yes. I chaired the committee that selected Nature Publishing Group to be the publisher of the *Journal of Neuropsychopharmacology*. Then, when we developed this *Review of Neuropsychopharmacology* concept, they came in with a gang-buster proposal, and so they are publishing that. I think that was very good, because we are now up to a several hundred thousand dollars in income from our publications.

WB: Have you been involved in other professional organizations?

JC: I've been also very much involved in Society for Neuroscience, almost from its beginning. I served on council. I was elected Treasurer and I was elected President for 1991-92.

I was able to get a NIMH minority training grant funded through the Society when I was President. I served as a Deputy Director of that for over ten years. Joanne Berger-Sweeney, who got her PhD with me and is now an Associate Dean at Wellesley, was the PI on the grant. At the end, we were

having Hispanics and African-Americans in MD-PhD programs at Stanford and Harvard. You could see that something had happened over a decade and I think we were a part of that something that created a situation where we are going to have minority members that will be very prominent in the neuroscience community.

WB: Weren't you the only psychiatrist that was ever President of Society of Neuroscience?

JC: I think I was the only practicing psychiatrist; Eric Kandell and Sol Snyder were also Presidents. At the time I was President, I was the Head of Child Psychiatry at Hopkins, seeing patients and doing research.

WB: Okay, would you say something about your family

JC: When I studied in Paris for junior year in college, in the group was a gal that came from Washington DC. When I was in medical school in Baltimore at Hopkins, she invited me down to DC for a party at her house and I met this incredibly vivacious and attractive woman, Genevieve. She was living in New York, so I was kind of bummed out about that. Then, a year later, I went to another one of these parties and she was there. I thought that "I'm not going to miss on this one," so I took her up to Baltimore and fed her crabs and, so, we started a relationship and I just knew that she was the one. I don't think she was quite as convinced.

WB: You convinced her.

JC: Yes, right. I was persistent. So, we married in between my junior and senior year of medical school. She had a degree in social work and so, we got by financially and it was great. Then, I went to NIH and she was working and I was getting paid. One of the problems that we confronted was, we weren't making babies and, so, we decided that we would adopt and we just let everybody know that we were interested in adopting. Another physician, who had been with my dad in the Army and they had remained friends out in the Midwest, said that he had a young girl who wanted to put up her baby for adoption, so we went out and we were there right on the day the baby was born. That was our first son, Peter, and it happened at my last year at NIH. In the lab was a PhD scientist from Vietnam. About six weeks after we had adopted Peter, she approached me and said, "I heard you are interested in adopting." Well, we just adopted a son, and she said, "My sister is head of Obstetrics in Saigon and she just delivered an AmerAsian boy, who is going to be in an orphanage." So, I remember driving that night with Genevieve and I said, you know, you don't want to have an only child, right? So, the next day, I called and said we'll do it. Well, it turned out to be very, very complicated. The Vietnamese did not want boys to get out of the country,

because they could be future soldiers. We went through a period of almost two years of trying to get Andrew out. We sent money to the orphanage. The Nun would write us notes about how Andrew was doing and sent a couple of pictures. I don't know if you remember, but five months before Vietnam fell, they started to evacuate the orphans. A plane crashed and a number of orphans were killed. But things started to move and we got a call from a social worker, who was flying out with 5 or 6 orphans, among them, Andrew. And so, that's how Andrew came to join us at the age of two. When Peter and Andrew were about three and a half, we decided for the first time to have a babysitter take care of them for a long weekend and we'd go to southern Maryland and enjoy ourselves. We went to this great Inn and I ordered oysters Rockefeller. Genevieve took one look at them and started throwing up and she just threw up the whole weekend. That's when we discovered that David was on the way. He was our third son. They are adults now, and they've been great. Peter manages a bookstore in Somerville, Mass. He's married to a very lovely lady, who is in academic publishing. Andrew is in his third year of medical school at Tulane and is interested in International Health. The youngest one, David, is married and lives in Baltimore where he also works in publishing.

WB: Sounds like a success.

JC: Yes, everybody is healthy.

WB: Could you say something about what you are currently doing, your current research?

JC: I am the PI on a Silvio Conte Translational Research Center in Schizophrenia. The focus of the center has been on the NMDA receptor hypofunction hypothesis. Neuroanatomically, we have focused on the hippocampus. It's really exciting, because it goes all the way from molecular modeling that we do through electrophysiology with John Lisman, who is a hippocampus electrophysiologist, Howard Eichenbaum, who is very elegant on memory tasks and behavior, through brain imaging with Debbye Yurgelun-Todd and to clinical trials with Dan Javitt and Don Goff. What we have been focusing on in my laboratory is making conditional knockouts of genes that encode proteins that modulate NMDA receptor function. And, in our most recent observation, we have shown that when you knock out serine racemase, there is no D-serine made and that seems to be the important co-agonist for the NMDA receptor in the cortical limbic regions of the brain. This is consistent with these risk genes that are associated with reduced availability of D-serine in schizophrenia. And, you know, your most recent finding is often your most exciting finding.

WB: It is a structural model.

JC: No, if you block NMDA receptors with, say, MK801, you'll get down regulation of these biomarkers; it's not structural.

WB: Molecular.

JC: Yes, what we think is happening is that these GABAergic interneurons get recurrent feedback from the pyramidal cells; the NMDA receptors are sensitive because the NMDA receptor on a GABAergic interneuron accounts for forty percent of the postsynaptic excitatory currents. So, we believe what happens is, that with the blockade of the NMDA receptors on these GABAergic interneurons, the pyramidal cells are disinhibited and since the GABAergic interneuron doesn't know that, they down regulate these parameters. So, it's a circuit problem.

WB: Okay, we are about out of time. I've got one last question and that is: project into the future. What would you like to see happen? What is going to happen, go out five, even ten years in this field? What's your projection fantasy?

JC: Well, the first thing that I'd really like to see, and I'm hoping that science will take us there, is complete parity for mental illness and addictions with medical illness, and recognized as major contributors to medical morbidity, and that there are risk genes for them.

WB: Is that a prediction that it is going to happen or that you'd like to happen?

JC: Well, I think it's going to happen. I think we'll find that the risk genes are, say, for major depressive disorder, also have actions in the periphery and that they can account for those interesting association between depression and diabetes and heart disease.....

WB: Cardiovascular disease.

JC: Yes, cardiovascular disease. You know, the brain isn't something over here and the body is over there. So, that's first, and the second thing will be true of any area of medicine. I think psychiatry and psychopharmacology will be personalized medicine to a very substantial degree. We know that what we are looking at, sort of like shadows on the wall of Plato's cave, is what our diagnoses are all about now.

WB: And, we are going to turn around and look out into the light.

JC: Yes, we are going to look out into the light and we are going to see the way.

WB: But, we're chained. We have to break the chains, and then look out.

JC: Okay, break the chains and we'll find there will be whole new ways of categorizing disorders and that the treatments will really be much more focused on etiology, genetic ideology, but also to a certain extent, environmental contributions to that. So, I think our diagnostic entities, like

schizophrenia, bipolar disorder, will get broken up into much more discrete subtypes. And, it's going to be an interesting challenge, I think, for the pharmaceutical industry. I personally think that the day of two billion dollar blockbusters that treats all things is going to disappear and it's going to be a hundred million dollar market for this drug that's a cognitive enhancer for twenty five percent of the people that we now diagnose with schizophrenia and not for the other seventy five percent. So there's going to be some fairly radical changes, I think, that are going to drastically affect the economics of medicine and the pharmaceutical industry.

WB: Okay, anything else for the future?

JC: Anything else for the future? I was at the ethics meeting today. I think we are really going to have to come to terms in some way with the relationship between the pharmaceutical industry, NIH and drug discovery. I don't foresee the day when NIH is going to be developing drugs and I do see pharmaceutical industry as having very strong science. It is much different from what it was twenty five years ago, when serendipity ruled the world for psychopharmacology. I think we are going to have to sort out what this conflict of interest issue is really all about. How can we work together without looking like we're on the take or being manipulated? And, unless we do that, I think our ability to develop drugs effectively for Society, for our patients, is going to be limited.

WB: Okay, let me just say, I've enjoyed interviewing you. It was fun. I learned a lot of things: your incredible career. You are one of the top people in the world in this area, totally active and totally at the top of your game right now, so, anyway, absolutely great.

JC: I've enjoyed being interviewed by you. It was great fun.

4. ELLEN FRANK

WB: I'm Dr. William Bunney, Professor of Psychiatry at the University of California, Irvine, and I'm interviewing Dr. Ellen Frank*, a Professor in the Department of Psychiatry, University of Pittsburgh. Dr. Frank is a leading clinical neuropsychopharmacologist. I wonder if we could start with you telling me a little bit about your training.

EF: Well, there is sort of an informal answer to that question and a formal answer to that question. Formally, I have a PhD in Psychology from the University of Pittsburgh and I had the sort of standard clinical psychology training offered in the seventies, but I think my informal training was probably every bit as important. I am the daughter of, I believe, a brilliantly talented social worker, who was one of the founders of the discipline of geriatrics, and one of the first people to recognize the problems of older individuals as different from those of younger persons, perhaps because she was originally trained as a human biologist and worked as a laboratory technician before entering the field of social work. So, I had a kind of informal training all the years I was growing up in my mother's home. Then, when Tom Detre and David Kupfer first came to the University of Pittsburgh, I was hired to be their research assistant. They were working on a project in which they were trying to write a primer for the initial interview in psychiatry that they titled *The First Encounter*. The way we worked was that I'd come to the Institute a couple of nights a week and sit down and listen to the two of them talk about the diagnostic interview in psychiatry. I'd take notes, write the stuff up and I'd bring it back the next day. But, what it really was was a nine-month seminar in psychiatric diagnosis with two teachers and one student. So, a lot of my training really came in an informal way by listening to them, and then, later on, by watching how they did research.

WB: What about college and other training?

EF: Oh, that! Well, let's see. I have a B.A. in drama from Vassar College in Poughkeepsie, New York, and a master's degree in English literature from Carnegie-Mellon University in Pittsburgh: very important to neuropsychopharmacology.

* Ellen Frank was born in Pittsburgh, Pennsylvania in 1944. A graduate of Vassar College, she earned a master's degree in English at Carnegie Mellon University and a doctorate in psychology at the University of Pittsburgh. She rose to the ranks of Distinguished Professor of Psychiatry and Psychology at the University of Pittsburgh School of Medicine and Director of the Depression and Manic Depression Prevention program at Western Psychiatric Institute and Clinic. She was interviewed in Waikoloa, Hawaii, December 11, 1996.

WB: OK, what created your first interest in neuropsychopharmacology?

EF: Well, growing up in Pittsburgh, I honestly didn't know that there was such a thing as a psychiatrist who wasn't a psychoanalyst, until Tom and David and the New Haven crew came to Pittsburgh. I had no idea that there was a science of treatment in psychiatry, but I became immediately fascinated by what they were doing. This was in the mid-1970s, when we first had what appeared to be highly effective treatments for depression and other major psychiatric disorders and models for testing the efficacy of these treatments in an experimental way. I was just completely captivated by this idea.

WB: What were the drugs that they were working on at that time?

EF: For depression, amitriptyline and imipramine, and for schizophrenia, the standard antipsychotic drugs. I also was fascinated to see that some of these drugs might treat something that the family therapists had been trying to convince us was purely intra-familial, such as Tourette syndrome. We certainly have a different idea about this now, but that these major drugs could actually have an effect on something like Tourette syndrome was a completely novel idea at the time. Those were the main compounds that I got to see in action.

WB: You've done some really outstanding clinical work. Tell us about the research that you've done. Just give us a little history of the research that you've done.

EF: I sort of came into this by the back door. My expertise was really in the psychotherapeutic treatment of depression and, actually, post-traumatic stress disorder as well, that we did not call post-traumatic stress disorder in the mid-1970s. My first research grant, which I got as a second-year graduate student, was on the treatment of rape trauma, which no one, then, was calling PTSD. I learned a lot in doing that study about how to do a controlled treatment trial of psychotherapy. So, when our department decided that a really important problem was the maintenance treatment of recurrent depression, I was asked if I would organize the monitoring of the psychotherapy part of that study. Well, as time went on, my role expanded and expanded and by the time the study was done, my responsibilities included running the clinic, in which the study was being done and, finally, running the study itself. The question that the study set out to address was whether we could find better methods for preventing new episodes of depression in individuals who had well-established histories of recurrence. Previous studies, notably that of Prien and colleagues, had demonstrated that active medication, particularly imipramine, was certainly better than placebo and that a tricyclic antidepressant was considerably better than lithium for preventing pure unipolar

depression recurrences. But, if you looked carefully at the outcomes from the Prien collaborative study, you saw that even the best treatment wasn't that good. About half of the patients were ill again at the end of two years. So, our idea was that if you added psychotherapy to pharmacotherapy, perhaps, you could have a better outcome. What we also questioned was, whether decreasing the patient from an effective acute treatment dose to a so-called 'maintenance' dose was the best strategy. We had the impression that probably it wasn't. So, we elected to study a group of patients, all of whom had had acute treatment with drugs plus psychotherapy, i.e., imipramine and interpersonal psychotherapy, and then randomly assign them to the combination of drugs and psychotherapy, pharmacotherapy alone, psychotherapy alone, or a monthly clinic visit with no active psychotherapeutic or pharmacotherapeutic intervention for a period of three years. What we found was that if you continue active imipramine at the same dose that was used to treat the acute episode, you have a highly effective means of preventing recurrence, even in patients who, on average, are having episodes every year and a half to two years. What we didn't see was any added benefit for psychotherapy in addition to what might be termed 'full-dose' pharmacotherapy, but I think, frankly, that's because we had such a good outcome with the pharmacotherapy. There was really no room to see an added benefit. What we did find, interestingly and quite surprisingly, was that monthly sessions of the depression-specific psychotherapy had statistically significant protective effect, not as good as continued medication, but certainly better, clearly better than just monthly visits with no psychotherapy. Gerry Klerman used to say, it wasn't a fair test because we used the highest dose of antidepressant and the lowest dose of psychotherapy in any trial ever conducted. But we clearly found that continuing an antidepressant at the same dose that gets the patient well, probably, keeps the patient well.

WB: Now, what impact do you think this has had, because this has clearly been supported?

EF: When I go around now and I do grand rounds and I meet with first and second year residents and they have the idea that the way to keep recurrent patients well is to keep them on their medicine, essentially, indefinitely, I feel that the message has gotten across. I think the study did two things. I think it served to reinforce a changed idea about unipolar depression, and that is, that it's a life-long disorder. I think that prior to the Prien study and our study, there was the impression that schizophrenia was a life-long condition, bipolar disorder was a life-long condition, but unipolar depression happened in these isolated episodes and we didn't see it as something that really required maintenance treatment. And, I think that attitude has changed.

WB: And, that's a change.

EF: I think so. I think so. I haven't been in this field long enough to have the whole history, but it seems to me to have been a change.

WB: And what were your hypotheses in this work?

EF: Well, our hypotheses were that the combination of pharmacotherapy and psychotherapy would be better than pharmacotherapy alone, but we didn't show that.

WB: But others have, I would think?

EF: Well, no, not really. There's yet to be, either an acute or long term maintenance trial that shows definitively that the combination is better than maximally effective pharmacotherapy. You can show that the combination is better than psychotherapy alone, but there's yet to be a study that shows that adding psychotherapy improves on maximally effective pharmacotherapy when your outcome measure is the proportion achieving a remission. Now, we've been looking at some of our own data and these are not controlled trial data, these are historical controls, patients in earlier studies, who got the combination, compared to patients in current studies, who are only getting psychotherapy or only getting pharmacotherapy and it does look like there is a slight advantage, not a huge one, a slight advantage for the combination. But, no one has yet pitted these treatments against one another in a big trial and shown an additive effect.

WB: Now, who were the major people, nationally and internationally, in this field that you've interacted with as part of your research network?

EF: Well, Tom Detre was a huge influence in my life. He was the person who showed me that this was a science, who had enough faith in me to ask me to write a grant as a first year graduate student, and then, give me the support to do it. David Kupfer was a huge influence in terms of teaching me ninety percent of what I know about how to set up and run and analyze a controlled trial. Myrna Weissman was an enormous influence because Myrna taught me that you could, and this was very important to me, that you could be an extremely serious scientist and retain your femininity. I can still remember the first time I heard her give a talk. I was just a lowly research assistant at Western Psychiatric and she arrived to give a research seminar in this diaphanous summer dress with that halo of blond hair, stood up and gave a perfectly organized talk and, then, responded to questions just with millisecond latency. And I thought, this is what I want to be when I grow up.

WB: A role model.

EF: Absolutely. But, I think we often miss to understand why it's so hard for women in this field. We so rarely saw, up there in front of us, a "like other" woman, doing what we would like to be able to do someday. And my daughter describes this experience, when she was a second year law student at Harvard, seeing a petite, dark-haired, dark-eyed woman up there teaching a law class. And, it was like a light bulb went on: I can do this.

WB: Well, where is your daughter now?

EF: She's an Assistant Professor at Marquette Law School. But, I think that that visual impression of a "like other," doing what she wanted to do was so important. There are just not enough of these around.

WB: OK, any other people who are important?

EF: Gerry Klerman was very important because he was the one who really taught me, and I sort of did not know, that psychotherapy research hadn't been about outcome. I couldn't understand why anyone would want to study anything other than outcome; I really didn't understand that. This was a new idea. And, I think I learned a lot about research design from just looking at studies that Gerry had designed.

WB: He was good at that.

EF: He was good at that. He had so much foresight in terms of what the important problems were. When you look at his first depression treatment study, it was a continuation treatment study. He already recognized that; he knew in the 1960s that this was a chronically recurring disorder and the issue was relapse and recurrence. So, he's been important. Those are the main people. They're all familiar, aren't they?

WB: Now, you mentioned the issue of a role model, a woman, female role model, but I know you've had interest, over the years, in the gender issue. I mean, it's obvious that this is a factor in depression. What has been your real involvement in that?

EF: Well, because I graduated from a woman's undergraduate institution that has always been, in its own way, a feminist institution, just at the time that the feminist movement was beginning, or the second feminist movement was beginning to take place. And, I came back to Pittsburgh from college, and within a couple of years, I was hosting a talk show on women's issues, which I did for seven or eight years.

WB: I didn't know.

EF: So, in that program, for seven years, I addressed a whole range of topics that had to do with women and women's concerns. So, naturally, in any field, in which I would have found myself, whether it had been psychology, psychiatry, literature, you name it, I would have been interested in the question of gender differences and how women are different from men and how their experiences differ from the experiences of men. I spent my sabbatical last year, primarily, trying to figure out why it is that women are so much more vulnerable to depression than men.

I've not found the answer, but it's something I've been interested in.

WB: Did you come up with something?

EF: Well, I have some ideas about why rates of depression take off so rapidly for adolescent girls, relative to boys. And, I think it has to do with the interaction between biologic and social factors in the age period, let's say, between ten and fifteen. But, it's too long a story.

WB: Now, in your research, are there new technologies, new instruments, new things that you had to develop in order to move it along?

EF: Well, I was part of a group, nationally, that became interested in specifying treatment delivery and, I think, part of that came from the idea that if we were going to compare psychotherapists across individuals, that we needed treatment manuals, that we need to be specific about how the treatment was supposed to be done. But, I think that also led to a specification of how pharmacotherapy should be delivered. I always like to say that we won't have the pure test of the pharmacotherapy efficacy until people can go up and get the active medication or placebo out of an ATM machine, that there's always the human factor in the delivery of pharmacotherapy and it has a big effect. So, I think an important set of tools for me were all of these manuals and treatment strategy descriptions that enabled us to do, what I think, were relatively well-controlled studies of the differences between pharmacotherapy and psychotherapy. Those tools enabled us to demonstrate in our long-term maintenance trial that the therapists who were supposed to be doing psychotherapy were really doing psychotherapy and the ones who were supposed to be delivering just medication clinic support, that's all they were doing.

WB: So, it was sort of a codification of what needed to be done?

EF: A codification of the interaction between the patient and the clinician.

WB: Do you remember when your first paper was published?

EF: I know when my first important paper was published. In 1978, I published a paper, based on an old data set that David Kupfer and Carol Anderson had brought from New Haven to Pittsburgh.

It was on the differences between couples who sought marital therapy and couples who sought sex therapy. And, then, Carol and I went out and gathered a population of happily married couples, couples who felt their marriages were working, and demonstrated that sexual dysfunction, as defined by Masters and Johnson, was pretty much rampant in these happily married couples. That paper appeared in the New England Journal of Medicine, which isn't bad for starters.

WB: Pretty good.

EF: They tortured me over it. You know, every word had to be rewritten.

WB: Do you remember your first scientific presentation?

EF: Ah, yes. My first scientific presentation was based on this data set from New Haven and it was at the American Psychiatric Association in May of 1975. I'd never given a scientific paper before. I had no degree. I hadn't even begun graduate school. I felt like a complete and total fraud. But I was a good enough intuitive psychologist to know that behavior rehearsal was an important part of settling yourself down, so I went to look at the room and stood up on the podium the day before my presentation. It was pretty...

WB: ...awesome, to say the least.

EF: Yes, but I got through my paper and nobody asked me any questions that I couldn't answer, so, if I was a fraud, they didn't know.

WB: What are you doing now? What is your current research involvement?

EF: Well, the questions really haven't changed very much. The T-shirt still says, "How Do You Prevent Recurrence?" I've become passionately interested in and concerned about manic-depressive illness and how poor our treatments are for manic-depressive illness, relative to our treatments for unipolar depression. So, I'm currently doing a study where we're looking at whether the combination of pharmacotherapy and psychotherapy, a psychotherapy that we've developed, which we think might address some of the etiopathology of bipolar disorder based on interpersonal psychotherapy, adds anything to the efficacy of well-done pharmacotherapy in the prevention of new episodes of bipolar disorder. As I mentioned before, in our unipolar study we really couldn't show added benefits for the combination of medication and psychotherapy, because even the drug alone-treated patients had very good social functioning, but bipolar disorder may be different. We're also doing a study that is another kind of follow-up to the original maintenance study. In that study, we showed that monthly sessions of interpersonal psychotherapy had some protective effect. So, we asked ourselves who would want nonpharmacologic maintenance, given that

pharmacologic maintenance works so well. The answer we came up with was women in the childbearing years, because there's a whole period when women are trying to conceive, carry and nurse a child when, generally speaking, all things being equal, you prefer not to be putting drugs into the system. So, we've been doing a study in which we are treating women acutely, with interpersonal psychotherapy alone, and then, randomly assigning them to weekly, bi-weekly and monthly maintenance IPT sessions, trying to do sort of the dose-response study of maintenance IPT. We're about four years away from finishing that one, so it'll be a while before we know the answer.

WB: Interesting. Are you using any of Beck's ideas in that study? He has his own approach to non-drug therapy.

EF: No. I actually started out very much as a cognitive therapy advocate. We used cognitive therapy in my original studies of rape trauma. I was trained to do CBT by Marika Kovacs, who was a direct 'descendant' of Beck. When I first learned to do CBT, I thought I'd found the Holy Grail. I was very skeptical of IPT, because it seemed like a very soft treatment by comparison. That's what my mother did. Not that I didn't respect what my mother did; I just didn't think it treated depression. Well, IPT is a very, very effective treatment. So, I've stuck with it; I'm an empiricist. I've stuck with what seems to work. And, I found that once you stop either drugs or psychotherapy, the effects of these treatments dissipate rapidly. We found that with psychotherapy it's quite possible to do maintenance or booster treatment. But, I don't think these treatments inoculate people against recurrence.

WB: Would you pick one of your findings, discoveries as the most important one? Is that possible?

EF: Well, you know...

WB: The biggest contribution?

EF: Well, I think the first long-term maintenance treatment study of which David Kupfer was the original PI, in which we demonstrated that there is a huge difference in terms of risk of recurrence between being fully treated and not being treated. That, so far, I think, is our major contribution. I hope we'll get to build on it.

WB: Are there times when you've been tempted to leave the field?

EF: Not for a minute. I wake up every morning and I can't believe that someone is going to pay me to do what I'm going to do today. Are there new questions I'd like to answer? Yes. Do I feel frustrated? The studies I do take nine and ten years. Do I feel frustrated when I think about the

fact that I can only do two or three more of these in my life? Sure. But, nothing has tempted me since I found this. It is like finding true love.

WB: I guess the answer is that you're happy with how things have turned out?

EF: I feel I've been very, very fortunate in terms of the kind of research environment that I happened to be in, to have had the kind of support that I've gotten from, not just from David and Tom, but from my colleagues and from the staff. Essentially, we still have the same research team that we had when we started the long-term maintenance study, in 1981. So, I've been blessed by really dedicated team members who stick with us in this work. And, I've been blessed to have really wonderful relationships with people at the NIMH and they've been extremely helpful.

WB: All right, you're a creative, imaginative person. I want you to think about the future, to think in the real world what would be ideally happening in your field in the future, and in the blue sky world, what could happen up there, at some point, in the future?

EF: Well, I think we're beginning to learn a lot from epidemiology about how these disorders progress and develop over the lifetime. I don't think, in my lifetime, we will ever come to true primary prevention in psychiatry the way the bacterial disease folks think of primary prevention, but we may get to the place where we can identify the early signs of Disease A, which almost always leads, later on, to Disease B, treat Disease A in its earliest form and prevent B from ever happening. So, for example, we know that almost all of the women who by age twenty-five have major depression, had an anxiety disorder as a child. Now, it's an empirical question whether if we could address that anxiety disorder at fourteen or twelve, we could prevent that person from ever going down this path. That would be something I'd like to see us do. I think we're on the edge of an explosion in terms of new compounds to treat depression. I think the SSRI's are just the beginning of a whole new range of treatments. But, I'm wondering whether we don't need to learn whole new ways of giving these medications. We've been giving them as though they were tricyclics. I hope there will be people who will step back and say; maybe this isn't the way to use these compounds. They clearly have an impact, but maybe there's a whole other treatment strategy that we ought to be looking for. Maybe the model that worked with respect to imipramine and amitriptyline for the prevention of depression doesn't work at all with these medications.

WB: You're talking about frequency, dosage?

EF: I'm talking about frequency and I'm talking about dosage. The idea with the tricyclics is pretty clear that you take the person up to the maximally tolerated effective dose and just keep

them there; but, maybe with the SSRI's, we need to start much lower and shift as treatment goes on. I think something may be happening over the course of time with these new drugs that the patient who's successfully treated, initially, with 10 mg, let's say, of fluoxetine, may need 20 mg to be maintained. So, I think, we don't really understand, yet, exactly how this works. We may think we know how they work at the receptor level, but what I'm interested in is what happens in the clinic. And, I think, as more and more of the treatment of the psychiatric disorders is being handled in the primary care clinics, we'll need even crisper models for how to use these drugs, because physicians don't have the time.

WB: That's another problem.

EF: I don't really have a clear understanding of all of what's going on in molecular biology, but I think it's not inconceivable that there may come a time when you can ask the question, would you wish that there was no manic-depressive illness. I think Kay Jamison has really raised that question in a very effective way. Would we want a world in which there were no more people with manic-depression? I think the answer is probably "no." Would we want a world, in which no one had schizophrenia? I think the answer is probably, "yes." Will there come a time when we can identify in these diseases in utero and alter things in utero? Would we choose to do that? These are not just scientific, but big moral and ethical questions.

WB: They may not be that far away.

EF: That's exactly right and the ethicists better get their act together, because we're going to be pounding at their doors.

WB: Are there things I've left out, things that you want to put on the record?

EF: No, other than I would like to say that I kind of got here by accident. I had good library and writing skills. This crew, Tom and David and Carol Anderson, came from New Haven to Pittsburgh and were looking for somebody who could read and write and fix up their manuscripts. I came in completely by accident. This is the most unplanned thing. It feels like a perfect fit. I feel incredibly fortunate to have gotten here. I do think about how my life would have turned out, otherwise. I was an undergraduate drama student; I spent a summer in Stratford-upon-Avon. That summer the Royal Shakespeare Company was doing both *The Jew of Malta* and *The Merchant of Venice* in repertory. Eric Porter was playing both of these roles, so I got to know him a bit. About seven years later, Porter was being interviewed by Alistair Cook on Masterpiece Theater during

an intermission in the Forsythe Saga and Alistair Cook asked him if he thought he'd been a success and he said, "Absolutely. I figured out what I want to do and I found a way to get paid for it."

WB: Good.

EF: And, in that sense, I feel like a success.

WB: Well, you sound like somebody that's in the middle of her career. You've got twenty good years of productive research that you've already put in and, probably, another x number of years to go in the future. OK, anything else?

EF: I don't think so.

WB: OK, I've been interviewing Dr. Ellen Frank, a Professor at the University of Pittsburgh, whose unique contributions to the field of neuropsychopharmacology are internationally recognized. It's been an honor to talk with you.

EF: Well, an honor for me, too.

5. J. CHRISTIAN GILLIN

WB: I am Dr. William Edward Bunney, Jr., currently Professor and Director of Research at the University of California, Irvine. I'm interviewing Professor J. Christian Gillin*, who is a professor at the University of California at San Diego. Chris is, in my view, clearly the outstanding sleep researcher in the world. He has that international reputation. He is known for the quality, for the carefulness with which he conducts research. Chris has been a pioneer in the field of sleep research and its relationship to neuropsychopharmacology. So, I'd like to start the interview by asking Chris about his training.

CG: Thank you Biff. I was an undergraduate at Harvard College and did my medical school training at Western Reserve in Cleveland. After my internship in Cleveland, I went to Stanford University, where I was a resident for two years in psychiatry, and then, in 1969, I went to the National Institute of Mental Health, where I was what we called a "clinical associate" and I initially worked in the laboratory of Dr. Frederick Snyder. But then I had an opportunity to collaborate with you. That went on for some twelve or thirteen years while we were both at the NIMH. Later on, I worked in the laboratory of Dr. Richard Wyatt. These were the two main places that I got my research training: in your laboratory with Dr. Snyder and in Dick Wyatt's lab in the NIMH Intramural Program.

WB: Were there new psychopharmacological agents and drugs of interest to you at that time?

CG: Maybe I should go back to when I was at Stanford and was developing my interest in sleep research. I had an opportunity to work for about three months in the laboratory of Dr. William Dement. At that time, there was great enthusiasm about the possible role of serotonin in schizophrenia. We had an idea that some of the manifestations of schizophrenia, such as hallucinations, might be related to a dysregulation of REM sleep, that hallucinations might be dreams that somehow escaped the confines of REM sleep. I did a little work with serotonin in Dement's laboratory and some animal studies. Then when I went to the NIMH and was working with Dick Wyatt, we were particularly interested in the role of serotonin and its relationship to

* J. Christian Gillin was born in Columbus, Ohio in 1938. He received his M.D. from Case Western Reserve School of Medicine and completed his psychiatric training at Stanford University Medical Center. He worked at the Intramural Research Program of the National Institute of Mental Health from 1971 until 1982, when he joined the Department of Psychiatry at the University of California at San Diego. Gillin died in 2003. He was interviewed in San Juan, Puerto Rico, December 10, 1996.

schizophrenia. We conducted a number of studies, giving 5-HTP or tryptophan in large doses to schizophrenic patients to see if it had any antipsychotic effect. It didn't really do too much. So that was a line of research that didn't go much further at the time.

There was an incident when I was a resident that had a major influence on my interest in neuropsychopharmacology. Once when I was on call, I got a call from the emergency room saying that there were four young people who had come in with an anticholinergic delirium. They were crawling the walls and were totally delirious, and I was trying to think what could I do for these kids. Remembering my pharmacology lectures from medical school, I thought if we could give them physostigmine that might reverse the anticholinergic effect of the scopolamine they had taken. It wasn't a drug that was available at that time. But shortly thereafter, by pure chance, I met an army colonel who was on sabbatical at Stanford, and his job in the army was to do research on chemical biological warfare. He had conducted studies in army volunteers given scopolamine-like drugs and had shown that physostigmine was effective in treating them. So, I had occasions later on in the emergency room to use physostigmine in some patients and it worked quite well. At about the same time, physostigmine was approved for treatment by the FDA. The cholinergic system has been one of the areas of my research all along.

WB: Why don't you tell us a little bit more about the cholinergic hypothesis of REM sleep?

CG: One of the interests I had when I started research in sleep was to understand what neurotransmitters were involved in the regulation of REM sleep. For a long time, we really didn't have a clue. But as I read the animal literature, it seemed that more and more data supported the idea that cholinergic mechanisms might initiate REM sleep. So we were trying to figure ways to test this, and after some false starts, we found the right dose and right way of administering physostigmine. When we gave it intravenously to normal volunteers during the first non-REM period of sleep, we learned that we could turn on REM sleep, and also that these REM periods seemed to be totally normal, i.e., did not differ from naturally occurring REM sleep.

WB: Wasn't this the first demonstration of that?

CG: In humans, yes.

WB: Right.

CG: A lot of this work was done by one of our former students, Dr. Sitaram. At the same time, we were doing our first studies on sleep and depression, and one of the key findings we had observed, as Dave Kupfer and others had previously, was that depressed patients had short REM latency.

These findings indicated that cholinergic mechanisms were involved. So we tried to figure out some ways to approach that and ended up developing a test we called the Cholinergic REM Induction Test; we gave a cholinergic agonist like arecoline intravenously to either normal volunteers or patients with depression while they were asleep and would measure how long it took to induce REM sleep. We found that depressed patients entered REM sleep more quickly after receiving this challenge than did normal controls. So that was a line of research, and a number of groups around the world have replicated our findings; Berger's group in Germany has done so on several occasions.

But certainly that's not the whole answer to understanding the basic mechanisms of sleep disturbance in depression, so we've returned to my earlier interest in serotonin, and right now we're trying a variety of techniques to understand how to study the role of serotonin in sleep in normal subjects and in patients with depression. One of the things we are interested in is the tryptophan depletion technique, pioneered by the group at Yale, headed by Pedro L. Delgado. We have some very interesting findings, which I think tie serotonin deficiency to sleep disturbance and maybe to the pathophysiology of depression.

WB: Were there other drugs that you were interested in working with?

CG: The two main substances in terms of basic pharmacology have been acetylcholine and serotonin, but in the course of our research we've studied many different drugs, including those that affected the dopamine system. We've looked at a whole series of antidepressant medications and had the very interesting finding that MAO inhibitors completely suppress REM sleep in depressed patients. When maintained on high doses, we found they could go for more than a year or so without any REM sleep. We've looked at a whole series of antidepressants in recent years. For example, with John Rush, we found one of the newer antidepressants, nefazodone, increased REM sleep in depressed patients, contrary to nearly all of the other antidepressants. So it raises an interesting question about whether increasing REM sleep might be good or bad for people. It might be harmful for some, and it may be good for people with, say, abnormal nightmares, such as in PTSD. We are going to look at some of these patients in the near future.

WB: Your lab pioneered looking at the effects of psychotropic drugs, particularly the antidepressants, on sleep parameters and, specifically, on REM sleep. Is that correct?

CG: That's true because it was very appealing that we had this electrophysiological measure that was basically non-intrusive; we would put people in the lab, give them medications to see how it

affected their mood or their psychiatric condition, and at the same time get some notion of what it was doing in the brain by using sleep parameters as an outcome measure.

WB: You casually talk about doing these sleep studies. My experience working with you in the laboratory is that this is a heroic effort. Why don't you comment on that?

CG: It certainly gives you an appreciation of need for sleep. I know you stayed some long nights in one of the studies we did together, giving L-DOPA infusions to patients with depression and normal controls. It is a very tough life. But as you grow older, you hopefully recruit energetic, enthusiastic young people who don't mind it as much as I do now.

WB: Maybe it is worth going over some of the hypotheses you were involved in creating and designing studies to test them.

CG: What we were doing in part was to move away from a mono-neurotransmitter hypothesis of psychiatric disorders or for the regulation of sleep. It's obviously an interaction of many different neurotransmitters, and we didn't really believe that acetylcholine was the primary mover in depression, even though that had been proposed in the past. What was much more appealing to us was the idea that there was a balance between cholinergic and aminergic mechanisms and that we would never really understand how the brain works or how any of these disorders are manifested, if we didn't begin to look at it in a multivariant rather than a univariant way. Using these probes was one approach to overcoming that narrow univariant conceptual outlook. So, we're still trying to develop techniques where we could give both probes to an individual and test the hypothesis of a balance between neurotransmitters. We're doing some studies, now, in which we are probing people with both cholinergic and serotonergic drugs, and our hypothesis is that there is some kind of correlation between the two; in a given individual you're tipping the balance in the case of depression. It's a bit like the notion of Parkinson's disease representing a balance between cholinergic and dopaminergic mechanisms. The major abnormality is probably on the dopaminergic side, but the cholinergic side is obviously involved.

WB: In addition to clinical research, you've been involved in basic animal research also. Do you want to comment on that?

CG: After we got interested in the cholinergic system, we realized that very little was known about the neuro-anatomical pathways or specific receptor systems that mediate cholinergic effects within the brain. I was fortunate to have a post-doctoral student, Peter Serramonte, who performed one of the first studies demonstrating pathways from the brainstem to the forebrain, which mediate

cholinergic mechanisms. We did other studies which pinpointed the effects of cholinergic mechanisms in inducing REM sleep, primarily mediated by muscarinic-M2 receptors. We've also done studies on the muscarinic-M1 receptors, both pharmacologically, and more recently, using in situ hybridization techniques to identify the specific RNA message that is expressed in demonstrating which specific muscarinic receptors are involved. I think it's the marriage between basic and clinical studies that is the most attractive way to advance the field.

WB: Are there new technologies that you had to develop, either in your clinical or basic research, which allowed you to move the field ahead?

CG: One of the things that maybe our group played a major role in was to develop methods for studying cholinergic mechanisms with physostigmine or arecoline, in which we had to give injections intravenously to humans, because the half-life of these drugs was so short. We found one of the key variables was at what time during the sleep cycle we had to administer it. It was quite revealing how you would get much faster induction of REM if you gave the physostigmine half way through a non-REM period than at the beginning. Again, this finding hinted at a change in the dynamics of the nervous system.

One other area that also fascinated me over the last ten or twelve years, which involved some of the collaborations with you, is brain imaging. That started when I was at the NIMH and we collaborated with Lou Sokoloff, Charles Kennedy and that group, and did the first credible study using the deoxyglucose technique on non-REM sleep in monkeys. We were able to measure on a quantitative basis in a very rigorous fashion what the rates of absolute glucose metabolisms were during non-REM sleep compared to the waking monkey. We found quite a dramatic drop in overall metabolic rate of glucose throughout the entire period of non-REM sleep. Later on, when your group and Monte Buchsbaum's moved to Irvine and I moved to San Diego, we were able to do a series of studies on humans in PET scanning with fluorodeoxyglucose. We were the first group having a very carefully controlled study with fluorodeoxyglucose of brain metabolism, both during REM, non-REM sleep and wakefulness.

WB: I think there was a similar study done before that on one patient in Cologne, Germany.

CG: That's right. Even our study was done in a very small group of subjects. But we had at least ten subjects in each of those three cells, so we were able to use statistical analyses. We also did a study of the effect of sleep deprivation on glucose metabolism in normal subjects. Again, I believe it was the first such study ever done. Another important issue I think has been neglected is the

basic mechanisms of sleepiness and what the effect of sleep deprivation is on the brain in performance and so forth. Human brain imaging will contribute a lot in the future to help understand those mechanisms.

Another interesting part of this story is the “antidepressant” effect of sleep deprivation in depressed patients. You certainly pushed it for a long, long time. I think you are one of the first investigators to really see the potential importance of sleep deprivation used as treatment for depression. We did the first study with fluorodeoxyglucose, before and after sleep deprivation in patients with depression. In about a third to a half of patients, sleep deprivation had a significant antidepressant effect. What we found in this particular study was that the patients who responded to sleep deprivation had an elevated glucose metabolic rate in the limbic system, particularly the anterior cingulate gyrus, that normalized with improvement. That first study was published by Joe Wu about four or five years ago, and now we’ve got a larger group and the basic findings, with some modification, hold up quite nicely. It’s an extremely strong experimental paradigm. If we could understand how sleep deprivation has an “antidepressant” effect, it would be a very important breakthrough. One could make a lot of generalizations from it for other aspects of the treatment of depression.

WB: I couldn’t agree with you more. When did you publish your first paper and what was it on?

CG: The first paper I published was on the use of physostigmine in anticholinergic delirium. Jack Heiser and I published that in the *American Journal of Psychiatry* in 1969 or 1970, as I remember.

WB: How many papers did you publish in the last two years?

CG: Maybe twenty or twenty-five.

WB: I’m trying to make a point that you’ve had a long career and that you are still active and going full steam.

CG: I still enjoy it.

WB: That’s an incredible credit to you.

CG: I hope I’ll be able to do research ten years from now.

WB: You’re a vigorous role model for people.

CG: Thank you.

WB: Are there other findings we haven’t covered?

CG: We covered the major areas. One of the things I’ve taken a lot of pleasure in, over the years, is working with young people who want to do research. We’ve had some success in people who’ve

gone through the lab. One of the things we started when I went to the University of California in San Diego was a Fellowship Program for training young psychiatrists to do biologically oriented research, particularly neuropsychopharmacology. We've been able to get funding through NIMH for that. It's been turned over to Michael Irwin recently, who is one of my colleagues, but I am still very much involved with that program. I usually have about five or six people in the lab, who are there as either post-doctoral or pre-doctoral students.

WB: Who are the people who had a major influence on you or you collaborated with during your career?

CG: One person was Bill Dement, who is a tremendously charismatic person, totally committed to sleep research. His enthusiasm always inspired me.

WB: And he made the first discovery with Kleitman about REM.

CG: He was certainly one of the very first people there.

WB: Wasn't he the first?

CG: Aserinsky and Kleitman are given the credit for the discovery of REM sleep but Dement came in very shortly after that and I think probably was the one who started the field more than anyone else. And Dave Kupfer has certainly been a very important person. He and I have been good friends over the years.

WB: So you've been active from almost the beginning of the explosion of interest in REM sleep.

CG: REM sleep was discovered quite a few years before I even went to high school, but I think I certainly got in as second generation. REM sleep was discovered about 1952 or 1953, something like that.

WB: So, you got in about fifteen years later. But that puts it in a historical perspective. For two thousand years, mankind was not aware of REM sleep and then Kleitman came along. If REM sleep hadn't been discovered, it would have been a different world for you, wouldn't it?

CG: My mother certainly didn't raise me to be a sleep researcher and I never heard of the field until I was in medical school. It's certainly been fortunate. The timing was good and I was able to get in a field that was still relatively young, there were lots of exciting questions to be answered.

WB: When you got into it, there were not a lot of people involved.

CG: No, there weren't. The Sleep Research Society had maybe a hundred or two hundred people, something like that, and now there are about thirty five hundred people who belong to the two major sleep societies in this country alone.

WB: It's an order of magnitude larger now.

CG: It has grown enormously, and the whole field of sleep disorders medicine has emerged. There have been tremendous advances in understanding the basic mechanisms of sleep, even in the past decade, in terms of the relationship to circadian rhythms, the basic mechanisms that underlie the circadian clock, the mechanisms that regulate the circadian rhythm of REM and non-REM sleep, and the mechanisms underlying the EEG. These are all major things.

WB: There are really two parallel bodies of scientific inquiry, those about sleep and those about psychopharmacology. You were one of the individuals who put those together and almost from the beginning merged the two disciplines.

CG: It's always been my hope that we could apply our understanding about sleep mechanisms to the understanding of psychiatric disorders, because sleep disturbances are such an intrinsic, prominent aspect of depression, mania, schizophrenia and many other disorders.

WB: And you've employed a new technology, PET scanning, in sleep research. So, three fields have been combined in your research.

CG: Absolutely. But I still consider myself primarily a psychiatrist. My goals are really to do something about psychiatric disorders and to understand them better. And I use sleep, as the window into the brain. I am also very interested in understanding sleep as a phenomenon.

WB: Before we finish, who were the major giants in the field of sleep research, regardless whether you did or did not collaborate with them?

CG: David Kupfer is someone who played a major role in drawing attention to the relationship between depression and sleep disturbances. He was the first person to describe short REM latency in depression. Bill Dement, I've mentioned already for his influence on the overall field. There have also been some basic scientists. I would say one of the most important people in my judgment was Allen Hobson, who was a psychiatrist at Harvard. He was interested in the fundamental mechanisms of sleep. He was on the Scientific Board of the Intramural Program at the NIMH and I used to talk with him a great deal. Bob McCarley was in that group and I think he's played a very important role in the development of my thinking.

There are several neuroscientists around the world like Barbara Jones, Mircea Steriade, Michel Jouvet, Dennis McGinty, Jerry Siegel, and Michael Chase, just to mention a few, who have been very important in the development of my thinking. Alexander Borbely from Zurich, Switzerland has been a close friend and a collaborator in a number of projects; he has a very broad

view of sleep, neuropharmacology and its relationship to psychiatric disorders. R.H. Van den Hoofdakker from Holland was one of the first in the mid-1970s to study the effect of sleep deprivation in depressed patients. He has played a major role in the development of my thinking; he has also been a good friend throughout the years. I probably don't remember everyone I should give credit to. But there have been a lot of people who've helped along the way. One of my collaborators was Wally Mendelson. He's now a member of the ACNP and professor of psychiatry at the University of Chicago.

WB: What you are telling us illustrates that like any field of science, there is a network of scientists working in the same area of research. You've been totally plugged into that network for many years and that has helped in developing your ideas.

CG: Yes, and certainly it was a very exciting time when we were at the Intramural Program of NIMH. One of my role models is Julius Axelrod. I was not fortunate enough to have the opportunity to work with him, but I was always very intrigued by the way he thought about problems and how he was always turning out ideas. We were able to utilize some of those ideas in our own research. Irv Kopin was a critical thinker; and Dick Wyatt a very imaginative person. We collaborated with Tom Weir and Norm Rosenthal on several projects. And Tom, Norm, and Anna Wirz-Justice taught me a lot about chronobiology that was important for my work. Since I've been at San Diego, Lew Judd has been a great leader and supporter of our research. I also have had the opportunity to work with a lot of interesting and bright people there.

WB: What would you select as your single most important contribution?

CG: I see my contributions more in linear progression. I have been interested from the beginning in the relationship between sleep and psychiatric disorders and the effect of pharmacological substances on both. It's not one of our studies but the cumulative effect that contributed to the development of the field. I'm very pleased I had an opportunity to work with functional brain imaging and to use that for studying sleep. We were among the first to study sleep deprivation with brain imaging and that area of research was also very exciting.

More recently I've had the chance with Marc Schuckit at USD to do some research on alcoholism and sleep. This was an area that hadn't been studied for twenty years or so. Marc is one of the foremost clinical authorities in alcoholism and he set up a beautiful system that allowed us to track people longitudinally. It's a carefully designed study that was done in carefully diagnosed patients. We were able to show for the first time that the sleep measures in the very early phase of

the treatment, like the first week of hospitalization, are good prognostic indicators. We could predict in non-depressed alcoholics with about eighty percent accuracy those who would relapse and who would stay sober three months after discharge.

WB: Are you happy with the way things are going?

CG: In general, yes. My career has been very satisfying. I've enjoyed the people I worked with. I still get excited by new ideas. On the negative side, we all face the uncertainties about whether there will be enough money or public support for research in the future or whether we're going to be able to attract the bright young people into the field that we need. But I hope I'll be able to keep working for a good many more years.

WB: What's going to happen in the future? Where is the field going? Will the field of sleep research connect with psychopharmacology and brain imaging? Tell us realistically and also your fantasy.

CG: I can see progress in several important areas. I hope we'll have a much better understanding of the neurophysiological basis of sleep and the neuropharmacology of sleep to use sleep as a sort of window for understanding psychiatric disorders. I think this research could be married with functional brain imaging, so that we would get more precise localization of which neurotransmitter systems and what physiological areas might be involved in the regulation of sleep in health and in disease.

From a public health point of view, I think understanding sleepiness in the context of circadian rhythm disturbances is a very challenging area. We are living in a twenty-four hour a day society now, where a very large proportion of the population is chronically sleep deprived partly because of work schedules and pressures, jet lag, work shifts, and I think it should be possible to play a role in helping people adjust to their schedules. Melatonin, for example, might be used to shift the clock in a desirable way, and there might be other ways that could be exploited. I would also be very interested in understanding the effect of sleep deprivation on cognitive processes, on our thinking and feelings. Another exciting area is the use of sleep as an outcome measure for neuropharmacologic probes. We can measure the effect of drugs on the brain in depressed patients and we might be able to use sleep as a way to tell whether a drug has an effect on the serotonergic system. We studied recently in a group of dysthymic patients maintained on SSRIs, the effect of tryptophan depletion and found that the REM-suppressing effect of SSRIs was removed without any effect on mood, i.e., without an exacerbation of depression.

WB: By the year 2005, we're going to have the human gene sequenced. Is that going to have an impact on understanding sleep mechanisms in normal subjects and psychiatric patients?

CG: The genetic approaches have not been applied successfully, as yet, in sleep research. But hopefully they will help us in two different diseases. One of these is narcolepsy. We know that narcolepsy is partially a genetically determined disorder in humans and in dogs, and there is some preliminary evidence that there are genetic markers, related to the HLA markers in the DR2 region, that may be related to narcolepsy. The other is a disease called fatal familial insomnia, probably one of the prion diseases, in which molecular genetic approaches will help.

WB: There can be psychotic symptoms in familial insomnia.

CG: There can be psychotic symptoms when it becomes a generalized disorder involving degeneration of the thalamus, primarily. Donna Giles' group is now doing a longitudinal study with some very promising preliminary data suggesting that this can be used as a genetic marker of depression. They found short REM latency in non-affected family members of patients with bipolar and unipolar depressive disorders. There is currently a series looking at c-fos activation as soon as animals enter into REM sleep or into non-REM sleep. I think we are going to see more and more studies of this kind.

WB: Chris, what have I left out? Are there any issues around your career, your experiences, and your view of the general field that you want to comment on?

CG: I think we are living in an exciting time. I'm happy that in all the different research areas in our field we are working together. I hope that it'll continue. Our greatest challenge is whether we can continue to attract bright young people into our field and whether we can get the necessary public support to make progress. I think the opportunities are there; there are much more opportunities than ever before. If we look back on the field of psychiatry, it has become much more sophisticated since the time we entered the field. And we have much more to offer to patients. We have scientific tools that weren't there before.

WB: I've been interviewing a pioneer in the field of sleep research, Dr. J. Christian Gillin. From this interview, one can get a feel for the breadth and intensity of his knowledge and understanding of our field, and especially, of the interactions of sleep research and neuropsychopharmacology. It's been an honor to interview him. Thank you.

6. LOUIS A. GOTTSCHALK

WB: I am Dr. William Bunney, Professor of Psychiatry and Human Behavior, University of California at Irvine. I am interviewing Dr. Louis A. Gottschalk,* who is Professor Emeritus of Psychiatry & Human Behavior at the University of California, Irvine School of Medicine and the Founding Chairman of the Department. He is one of the premier neuropsychopharmacologists in our field. Louis, I would like to ask you, could you tell us a little bit about your training?

LG: Yes. I was born in St. Louis, Missouri, and I went to university at Washington University in St. Louis. I attended undergraduate school there. As I reflect on it now, I had the good fortune of having some very inspiring scientific educators as an undergraduate. Then, I went to the Washington University Medical School, where, I didn't realize it at the time, I was being programmed by a number of Nobel Prize laureates. At Washington University undergraduate school, there was Arthur Holly Compton, a Nobel Prize winning physicist. At the Medical School, I was a student under Carl and Gerty Cori, Nobel Prize winning biochemists and Joseph Erlanger, a Nobel Prize winning physiologist. I didn't know it, but I just seemed naturally to be molded and shaped into doing a lot of research.

Beginning as a medical student, I had a position working as a research assistant, funded by the Josiah Macy Foundation, under some famous professors in the Department of Neuropsychiatry. There was David Rioch, whom I believe you know. The neuropsychiatry department was headed by John C. Whitehorn, who, already back in those times, had a neurobiochemical view of the etiology and pathogenesis of neuropsychiatric illnesses. And another interesting person in that department was a man that did the first frontal ablation experiments in animals; his name was Carlyle Jacobsen, Ph.D.; and he did these studies while he was still at Yale University. In any case, that's where I got my medical school training. I did internship in straight medicine at Washington University, Barnes Hospital. In those days – it may happen again – the departments of psychiatry

* Louis A. Gottschalk was born in 1916 in St. Louis, Missouri. Gottschalk earned his M.D. at Washington University in St. Louis and his Ph.D. from Southern California Psychoanalytic Institute. He completed an internship in Medicine and a residency in Neuropsychiatry in Barnes and McMillan Hospitals and post-graduate training in electrophysiology in the Neurology Department at Washington University. Following this, he served in the U.S. Public Health Service in Fort Worth, Texas and in the Intramural Research Program of National Institute of Mental Health in Bethesda, Maryland. He subsequently held faculty positions at the College of Medicine, University of Cincinnati. He was the founding chairman of the Department of Psychiatry and Human Behavior at University of California Irvine College of Medicine. Gottschalk died on November 27, 2008. He was interviewed in San Juan, Puerto Rico, December 10, 1996.

and neurology were together in one department. So, my residency was in neurology and psychiatry at Barnes and McMillan Hospitals at Washington University, St. Louis. Then, I think in 1947, I had to go into military service; and I was invited to transfer from the US Army, in which I was in the reserve corps during my internship and residency, to the United States Public Health Service, USPHS. As a matter of fact, I had a couple more years of accredited neuropsychiatric training, while I was stationed at the United States Public Health Hospital in Fort Worth, Texas. This hospital, which was a so-called “narcotic” hospital, a 2,000 bed hospital on 10,000 acres, had been transformed into a neuropsychiatric hospital to diagnose and care for neuropsychiatric casualties resulting from military service during World War II. I was one of many psychiatrists from the USPHS and the Navy looking after these neuropsychiatrically disabled Navy and Marine Corps service people, there. I had some more training in Chicago, Illinois in child psychiatry at the Michael Reese Neuropsychiatric and Psychosomatic Center. There, I also ran the EEG, electroencephalography, laboratory. In those days, in the late 1940s, it was still in style to get psychoanalytic training. I got that kind of training at the Chicago Institute for Psychoanalysis in child and adult psychoanalysis.

WB: You had some impressive mentors along the way, people who were really giants in the field.

LG: I was lucky; I really was. In Chicago, I worked under Roy R. Grinker at Michael Reese, and at the Institute for Psychoanalysis, I trained under Franz Alexander and Thomas French. I was lucky and didn't realize it.

WB: What got you interested in psychopharmacology?

LG: I was programmed very young, I think, to do research, and when psychoactive drugs came along, I was right into neuropsychopharmacology, very interested to learn more about them. That was about the time chlorpromazine came along in, probably 1957, or something like that. And it was also the advent of the benzodiazepines. What happened was that after my training in Chicago, I went to the National Institutes of Health. I was, in fact, the first research psychiatrist at NIH. It was in 1951, and again I encountered David Rioch, who was Chief of Neuropsychiatry at Walter Reed Army Hospital. In Chicago, I got interested in epilepsy and the trigger mechanisms of epilepsy in children. I took a group of epileptic kids, who were on anticonvulsant drugs, in whom the anticonvulsant drugs were not being effective with regards to their epilepsy. I tried psychotherapy, play therapy or other types of therapy, and lo and behold, for many of them their seizures disappeared. And I wrote and published those findings. So, when I went to the National

Institutes of Health, while I wondered what kind of research I was going to do, I went to Walter Reed Hospital and found some more patients that had epileptiform paroxysms in their EEGs. I thought, well, maybe I can find out what happens if you just have these patients free-associate while you are getting their EEGs. This idea came to me because I had had psychoanalytic training. I selected patients who had paroxysms of abnormal EEGs and I found out that some of those people, when they spoke about emotional things, showed more paroxysms.

At that point, it came to me that one of the most inexact areas in the field of psychiatry was dealing with interviews and the things that people said and the ways in which they said them. I decided it would not be a bad idea to try to develop more objective ways of arriving at accurate measures of anxiety or hostility, as well as how schizophrenic somebody was. That diagnostic achievement is generally accomplished through the neuropsychiatric interview and the content and form of language. So, it was there that I started to get into the measurement of neuropsychiatric states and traits from the content analysis of speech and verbal texts. And when I left NIH to become Research Professor of Psychiatry at the University of Cincinnati, some of the new drugs were being developed by the pharmaceutical industry and coming on the market. I got into trying to decide how to measure the effects of psychoactive drugs. I actually did some early clinical trials to determine whether or not drugs like diazepam (Valium) or chlordiazepoxide (Librium) might indeed be anti-anxiety agents. We did placebo-drug studies and we got five minute speech samples, which would measure objectively, with a method I had developed, whether or not subjects were less anxious when they were on the benzodiazepines. And these were the early psychopharmacological studies.

WB: How did you come up with the idea of the five-minute speech sample? I know this was something you developed and expanded on very successfully.

LG: It was. I can remember very clearly, at the time I was working at Walter Reed, interviewing epileptic patients and non-epileptic patients who had abnormal paroxysms on EEGs. And then I reflected that there are very sensitive technologies for measuring accurately many neurobiological phenomena, using biochemical measures and physiological approaches, such as recording brain waves, but we have no very accurate means of measuring the magnitude of various psychobiological states. There is, of course, the diagnostic interview, and the neuropsychiatrically focused diagnostic interview, which require a verbal dialogue. And at that point, I decided, hey, this is it! This could be a tough research field, but why not get into this area? I had also been an

English major, as well as a biology and chemistry major at undergraduate school. And that background facilitated my getting into the measurement of neuropsychobiological dimensions. I thought it would certainly have some use if a reliable and valid testing procedure could be developed. The challenge was that the development of such a measurement procedure would have to go through many stages.

I should, here, give some acknowledgment to a person I met at the University of Cincinnati, Goldine C. Gleser, who had specialized in measurement psychology. She had a doctorate degree, a Ph.D. She had also been a math major. She helped me on the statistical side of some of the problems to be solved in developing a measurement tool for detecting and assessing the magnitude of various psychobiological states. I do not think that I should get into more detail about statistical problems, but these will come up again, for I can see that the research areas I have gotten into, especially with drugs and other biochemical factors in neuropsychiatric illness, have followed me. In any case, I have continued to persist in working on the content analysis of language and have developed a computerized method of doing this, because I sincerely believe that in time, instead of psychiatric interviews or the use of various adjective check lists or other methods of measuring the magnitude of various psychological and psychiatric states, we will be using the computer, and we will actually use voice recognition. I am working on that now, but I've digressed a bit.

WB: No, I think that is one of the central issues, and you've made a major contribution with this. And, if I understand, this has to do with the diagnosis of emotions and has been used to follow behavioral change after medications. Is this correct?

LG: Absolutely right. I have kept following those ideas. As I think about it now, I do recall some of the people at Washington University Medical School, James Bishop, a neurophysiologist, David Rioch, who inspired me. Those fine neuroscientists, the way they thought, and the way they pursued things, I think got transferred and internalized by me. But, in any case, with regards to psychiatric drugs, I did get involved after a while in looking at the blood levels and the pharmacokinetics of psychoactive drugs, such as the benzodiazepines.

WB This was in Cincinnati?

LG: This was in Cincinnati. And, I found that if you had too low a blood level, you did not get any definite antianxiety effect, but over a certain blood level, there was this significant correlation between the anxiety scores, that is, a reduction in anxiety scores derived from my Content Analysis Scales and the blood level of the benzodiazepine, as well as the half-life of the benzodiazepine. I

also found that some of the benzodiazepines produce cognitive impairment, or at least impairment of recent memory, and that's related to blood levels. And from that, I got into looking at the effects of some of the major tranquilizers on schizophrenia, like thioridazine and mesoridazine. I found that the blood levels of those drugs, up to a certain extent in some schizophrenic patients, did correlate positively with an improvement. About a third of those schizophrenic patients did not have a very favorable response to those major tranquilizers, but two-thirds did.

WB: Now, your Content Analysis Scales have had international acceptance, as I understand it.

LG: Yes, one might expect they would. The German neuroscientists got interested in that sort of methodological approach and they have borrowed and used my ideas. They published a number of books using my content analysis methodology. The Chairman of the Department of Psychiatry in Hamburg, Germany told me that he and his colleagues got a million dollar research grant from the German government to test and apply our content analysis methodology to their neuropsychiatric research. And, since then, their studies have been published. The procedure has been published in Spanish in Chile, and in many other languages, in Norway, Poland, Australia, Italy, the Netherlands and Germany. And lately, people from other countries have also asked us whether we have a computer program in their language to do this. It is rather awesome that they would ask such a question, because computer programs are not readily transformed and adaptable to other languages.

We are currently working on a computer program that will handle the Spanish language because such a large percentage of the world's population speaks Spanish. But, yes, it has been shown that the norms that we have in normal individuals, free of mental or physical disorders, for anxiety and hostility, are not any different from the norms in Norway, Australia or Germany.

I suspect and think there's a difference in a country like Poland. I have had a visiting professor that lived there, who is coming to visit us again, and she found, and I am not surprised, that having suffered the ravages of war, the norms there for anxiety run a little bit higher than the American norms. But, yes, there's been a great deal of international interest in our methodology.

WB: Is that translatable? Is that the issue?

LG: Yes, it is, but not the computer program.

WB: It's a major effort in itself to translate that. Are there specific hypotheses that you've tested in some of this work?

LG: Yes. Well, some hypotheses. I think an obvious one was that blood levels of a drug should relate to the clinical effect. That is, within certain parameters, true. But if the blood level is too low, we have found out the drug is not going to have an effect. Also, you can give too large a drug dose, and we did find that above a certain blood level, a drug produces no more favorable clinical effect. That's for immediate effects of the drug.

And there was another hypothesis that I noticed at these meetings that has not had much effect yet in neuropsychopharmacology. That is, we got interested in the finding that thioridazine or mesoridazine, in some people, produce adverse cardiovascular effects, cardiac irregularities. And at the time we were studying those phenomena and getting electrocardiographic measurements and drug blood levels on patients, we got the idea to find out whether there are any differences in the psychoactive drug metabolites in people that get these cardiac irregularities. And lo and behold, we did discover that a metabolite that is not active psychoactively, sulfaridazine, does have an adverse cardiovascular effect. Those individuals that had the cardiac irregularities had elevated sulfaridazine, at that time. We were excited about that, published the finding, and tried to get the drug companies to provide further financial support so we could study the biochemical basis for the adverse cardiovascular effect of sulfaridazine. But, they were doing so well marketing their drugs that they would not fund it. But, I mention it now because the whole area of abnormal effects, side effects, I think, will be studied, perhaps, more and more. I think we are caught so much in the excitement about the favorable effects of drugs that the possibility that a drug's metabolites in everybody may be slightly different, except perhaps for identical twins, has not been focused on. We do metabolize these drugs slightly differently and subtle drug-metabolite effects are sometimes cardinal and important, so they can influence or obscure findings. That might become more and more important but has not been followed up very much. So that was one of the hypotheses we had; namely, that some of a pharmacological agent's metabolites, which are not psychoactive, might have other somatic and biological adverse effects.

WB: Do you remember when you published your first paper, or presented it?

LG: Oh yes, I think that was probably out of medical school. It was in psychosomatic medicine and not on psychoactive drugs. It was on vasomotor conditioning in human subjects. I did some of the research while I was a medical student. We found out by using classical conditioning that some people are very easily conditioned to have vasal constriction, and if you measure blood flow in the fingers with one or two faradic shock treatments to one hand, some are and some are not

conditioned. That got published, I think, around 1946 or something of that sort. We're pretty proud of it and it probably does have some importance, indicating that we are quite different in our capacity to be conditioned; that was a conditioned response to turning on a light. And some people who were conditioned just to a couple of reinforcements, continued to have vasal constriction if a light was turned on. No wonder some people get bad hypertension and some don't. There are probably genetic and other differences.

WB: Now, I know you're still active in doing some research. Can you tell us a little bit about what you're doing now?

LG: Yes, I'm still involved and I'm delighted that our own department has a brain-imaging center, and I know you are too, because we did do a fair number of studies on brain imaging and PET scans. We did look at the relationship of anxiety, hostility and dreams recently, with Ernest Noble, who was formerly at the University of California Irvine (UCI). We've done a study with PET scan, showing that people with the A1 allele, who are normal and who have no psychiatric history of drug abuse, alcoholism or obesity, themselves or in their family, have significantly different PET scans from people who don't have that allele. We would have never been able to do that if we hadn't had a PET scan in our own backyard.

Another study that I think is related to neuropsychopharmacology, which was published in 1991, showed that, of all things, manganese was elevated in the hair of violent criminals, compared to controls. I didn't think much of that paper, but we published it because there was no question about the finding. I didn't believe it the first time. I thought it was chance, so we got another sample of criminals and controls and it showed up in the second sample. I was still pretty skeptical, being a Missouri boy from the Show Me State. So we got a third sample and it showed up again. The puzzling thing about the paper and the finding was that we had empirical findings without any hypotheses. Since then, the Japanese and others have shown that manganese does lower the serotonin level in the brains of rats, and there have been a number of other studies replicating our finding. We are applying for a grant. It's going to the neurochemistry and biochemistry program of NIMH. I can't believe that one little element would be a big factor in the problems we're plagued with in our society, namely violence, but it may make some contribution. So we're into that. The research is going to have to be in an animal model, and I'm not unhappy about it, because we can control everything. That's one area.

Another area does relate to content analysis. There was an advertisement by the National Institute on Drug Abuse, soliciting grant applications on computerized neuropsychiatric testing software. Well, I thought, that was just built for us. What they want is software that will pick up cognitive impairment in people who have been involved in drug abuse. So, we've gone far.

Whether we'll get it or not is something else. One way or the other we're going to do that. We're into that area and I think we have a pretty good chance to get the grant. Who knows?

WB: Well, I often think, once a researcher, always a researcher. How many papers have you published?

LG: Well, I've got over two hundred papers and two hundred journal articles and about twenty-six books.

WB: Well, it's impressive in a fifty-year span and you're still going strong.

LG: I have a problem and I bet the Bunneys are going to have it too, namely, I wouldn't know how to retire. I think it's a problem.

WB: Now, who were some of the important people, not just in the beginning of your work, but along the way, that you interacted with working in the same area, where colleagues were important for you to communicate with?

LG: Well, over the years, I'm still going to flash back to some of those mentors, back at Washington U and in Chicago, who certainly were internalized by me. I was probably more carried away by them that they are with me.

WB: You still see the influence of psychoanalysis though. You have that concept internalized, which I also happen to believe in.

LG: Well, by internalized I mean that they're in the protein substance of my brain.

WB: I know what you mean.

LG: And the psychoanalysis thing, although I'm still a training analyst, I must say that I figure it's pretty much an art form, and I'm disappointed that it hasn't lent itself to an empirical approach. But it probably has influenced my willingness to listen to people for a long time, as it probably has influenced you. By internalize, I mean in a biochemical way. Oh, I think of various people in Cincinnati, Arthur Mirsky, a biochemically oriented researcher, and Maurice Levine for that matter, who made it possible for me to do research, and was encouraging. But at the University of California at Irvine, there were many people in the medical school who made it possible to do

research and also try to run a department. As a matter of fact, if I hadn't been able to do research, I don't think I would have been able to tolerate the administrative problems. There have been a lot of people involved in looking at the relationship of pharmacokinetics and chemical response and I edited two books on the topic and these were both under the imprimatur of the American College of Neuropsychopharmacology. It isn't a big or very important area these days. Everybody can get blood levels now. I'm impressed with this particular ACNP meeting. But what carries me away here, is the genetics and its role in psychoactive drugs and so on.

WB: If you had to list one thing, what would you consider your biggest contribution to the field of science?

LG: It's hard to pick one thing, but if I had to, it's a preoccupation with the accuracy and the precision of measurement, whether it's a measurement of psychological states and traits from speech, or the accuracy of measurement from blood levels of psychoactive drugs, you know, ranging from radioimmune assay to gas chromatography. I think I've been occupied with developing or asking for the best or most precise and ingenious methods of measurement. It seems to me a lot of big discoveries have been made from the microscope or the telescope. You were instrumental in bringing a brain-imaging center to UCI and I'm fascinated by that, too. I can't say that the brain imaging center is my contribution, but I certainly go that way. And, I do question the accuracy of the measurements. So I think a tremendous curiosity and insistence on objective and accurate measurements is one of my contributions.

WB: Okay. Were there any times that you were tempted to leave science, to leave research, job offers that would have taken you, either out of the field or into too much administration?

LG: No, just like today, I can't imagine life with retirement and not doing science. And, administration, I had a taste of it. It was fun to have the opportunity to develop a department and get it started, but I've avoided accepting positions of too much administration, because I thought it would take me away from science.

WB: Well, you were the founding Chair?

LG: Right.

WB: At the University of California, Irvine Department of Psychiatry.

LG: And, I notice that you, too, are able to keep your activities in the science area and avoid too much administration. It takes one to know one.

WB: Are you pleased the way things have turned out or unhappy?

LG: Oh, you mean in my career?

WB: Your career.

LG: I'm pleased the way it's worked and I would like to continue the present and the way it's working. I have a phobia of retirement and I think I'll keep going as long as I can, because it's such a fascinating field. I can't think of anything more fascinating.

WB: Okay, now where do you see the field in neuropsychopharmacology going in the future?

What's in the realistic future? What's in the blue-sky future? What's your vision?

LG: Well, I think, in one area that I've made a very original contribution is the diagnosis of mental disorders and nervous problems from language. I think, eventually, that's going to be possible from just voice recognition.

WB: What do you mean by voice recognition?

LG: The way that my content analysis measure works is, the material is tape recorded and then the typescript is put on a diskette and into a computer program known as LISP, which comes up with content scores on twelve different scales.

WB: You mean, like anxiety and depression, that kind?

LG: Anxiety, how schizophrenic someone is, how much cognitive impairment and how psychotic. The trouble is that takes time. Somebody has to type what is said. I think it's going to be possible, in time, to take speech, even with hesitations because they get scored too, to directly program speech or verbal texts for the computer.

WB: Without the intermediate typing?

LG: Without the typing. Yes. And, that's being done now. The problem is that the computer has to learn somebody's language. We're getting new software. I got software a couple of years ago from IBM but it was very picky, finicky and imprecise. The new software is going to be broader and more accurate. The advances in computer technology are so fast, I think, that's going to be relevant. You may think what's that got to do with neuropsychopharmacology? Well, it's going to shorten some aspects of the diagnostic process. It's going to make it more precise. And combining that with the very amazing and encouraging advances in translating genetic differences to understanding differences between various organisms – subhuman and human – it's going to help us predict which people are especially vulnerable. And, I do think, there's going to be a more successful application of drugs and treatment for individuals, and it's going to be a combination of these things. Our technology is really going places. The biggest problem is going to be, can it

be funded adequately. But that's another question. I'm a strong believer that we're on the right track. We're making tremendous advances, not just in psychiatric illnesses, but in software programs like this. Some of the illnesses are neurological, say, multiple sclerosis and so on, and the interaction of genetic and environmental factors is well attended to. So, I'm very optimistic that we're going to continue to see tremendous advances in our field here.

WB: You see more accurate diagnosis, a more accurate tailoring to active treatment modalities in the future, and then, eventually, an impact of genetics.

LG: Right.

WB: Now, what have I left out?

LG: I think you've covered everything.

WB: Anything else you want to put on the record?

LG: No, I think you've covered things very well. I really don't have much more to say, except I'm riding high on the continuing opportunity to do research and am very happy that, at least in my genes, the Alzheimer's gene is absent or not playing a big part. I think it's very fortunate and I thank whoever is responsible for this.

WB: Okay. So, I've been interviewing, today, Dr. Louis Gottschalk, professor at UCI. He has had a distinguished career, spanning over fifty years from the introduction of neuroleptic drugs through to the present time. He continues, actively, in research. He's known many of the great people in the field of neuropsychopharmacology and it's been an honor to interview him.

LG: Thank you very much, Biff.

7. SALOMON Z. LANGER

WB: I'm Dr. William Bunney. I'm from the University of California, Irvine. This is the Annual Meeting of the ACNP, 2008. We are in Scottsdale, Arizona and I will be interviewing Dr. Salomon Langer*. Tell me where you were born and something about your background.

SL: I was born in Buenos Aires, Argentina many years ago and my family came from Poland. In fact, they immigrated to Argentina in the early 1930s and this is how they were saved from the Holocaust during the Second World War. I went to school in Argentina and graduated as a medical doctor. After my internship I came to the United States on a Rockefeller Fellowship and got my post-doctoral training in pharmacology at Harvard with Ullrich Trendelenburg for four years, to be followed by two years in Cambridge, England with Marthe Vogt. That explains, to a large extent, my early interests in autonomic pharmacology, transmitter release and in drugs acting on these systems.

WB: Do you want to tell me a little more about your mentors?

SL: I was very fortunate to do my doctoral thesis in Argentina under Dr. Bernardo Houssay, who won the Nobel Prize for Physiology and Medicine in 1946. My biggest chance was when I hit the jackpot with Ullrich Trendelenburg at Harvard. I was the only post-doc, so I had him fulltime for the first year and it was so much fun and enjoyment I stayed for nearly four years. By the end of my stay at Harvard, my main interest was working on norepinephrine release and this is why I went for two years to Cambridge, UK to become familiar with the appropriate laboratory techniques used in this research. Having Marthe Vogt, a well-established and famous pharmacologist, as my tutor was another jackpot and I'm extremely satisfied and happy that my training happened this way.

WB: You really had an incredible experience, in terms of your training and mentors. Can you tell

* Salomon Z. Langer was born in Buenos Aires, Argentina. He earned his M.D. and did his doctoral thesis in Argentina under Dr. Bernardo Houssay, a Nobel Laureate for Physiology and Medicine (1946). He received postdoctoral training in pharmacology at Harvard University with Ullrich Trendelenburg on a Rockefeller Fellowship in 1963-67, followed by two years in Cambridge, England with Marthe Vogt. Subsequently, he started the Institute of Pharmacological Research at the University of Buenos Aires and then joined Synthelabo in Paris, France, first as Director of Biology and eventually, President of Research and Development. He continued his involvement in pharmaceutical discovery with leadership roles in Swedish and Israeli pharmaceutical companies. He was interviewed in Scottsdale, Arizona on December 8, 2008.

me what psychopharmacology was like at that point in time?

SL: Most of my studies on norepinephrine release were carried out on peripheral tissues. At that time, I was beginning to cross the blood brain barrier and became interested in the CNS. I knew full well it was extremely complicated but, nevertheless, made up of many similar units as in the peripheral nervous system.

WB: What years were these?

SL: This was in 1969; the period at Harvard was 1963-1967 and Cambridge, England was 1967-1969. It was then that the idea of regulation of norepinephrine release developed and I moved back to Argentina for seven years. I started the Institute of Pharmacological Research at the University of Buenos Aires and published the first papers on presynaptic receptors and their role in the regulation of neurotransmitter release, in that case norepinephrine.

WB: Who were some of the scientists that had a major impact on you?

SL: In addition to the mentors I named before, I must mention Julie Axelrod, and I had the privilege of meeting Sir Henry Dale, while I was in England, J. H. Burn and many of the pharmacologists at Oxford, which maintained a superb department of pharmacology. At Cambridge, I worked with Leslie Iversen for one day a week.

WB: When he was with Merck?

SL: No, this was before that, at Cambridge University, between 1967 and 1968.

WB: That was long before Merck.

SL: Yes, absolutely. So, these were the scientists that influenced me but, in addition, I must mention Norman Weiner; while I was at Harvard, we did some work together.

WB: And, with Julie Axelrod, what interactions did you have?

SL: Julie visited our research laboratories in Buenos Aires in the early seventies and subsequently, when I worked at Wellcome, UK, I received a Guggenheim Fellowship and spent time at NIH with him.

WB: When was that?

SL: That was in 1976.

WB: I was still there at the time. Were there other scientists you were interacting with that were critical?

SL: I must mention Jim Black and John Vane. Jim Black, because he was pioneering the classification of sub-types of receptors, when I discovered the alpha-1 and alpha-2 receptor

subtypes. It seemed unusual to me that an alpha receptor agonist would inhibit release of norepinephrine, which acts on the same postsynaptic alpha receptors producing vasoconstriction. By carefully categorizing these alpha receptors, it turned out there were two different sub-types. In 1974, it was the first description there were alpha-1, alpha-2 subtypes based on physiological evidence and the relative order of potencies of agonists and antagonists. It took about twenty years more for these receptor subtypes to be cloned, expressed and characterized by molecular methodology that confirmed alpha-1 and alpha-2 receptor subtypes were completely different classes of receptors with different second messengers and additional subtypes, namely alpha-1, alpha-1a, alpha-1b and alpha-1d, and for alpha 2, a, b and c subtypes.

WB: So, your initial papers were really landmark publications.

SL: In fact, the 1972 paper on Presynaptic Receptors was chosen by the British Pharmacological Society as one of the 35 most important published by the *British Journal of Pharmacology* during the past century.

WB: Fantastic!

SL: Yes.

WB: What were the early drugs you worked on?

SL: Of course, they were acting on alpha-1 and alpha-2 receptors as agonists or antagonists. There were not enough alpha-2 subtype drugs early in the game, except for clonidine and yohimbine, and they were not sufficiently selective. On the other hand, alpha-1 agonists like phenylephrine and antagonist drugs like prazosin were quite selective for alpha-1 subtypes. Thanks to those drugs, I could characterize the two sub-types of receptors. Then we asked whether norepinephrine release was modulated by presynaptic receptors and if that phenomenon could be observed for other transmitters, as well. It turned out that in the central nervous system, dopamine release, like norepinephrine release, was equally modulated presynaptically. For dopamine, the presynaptic receptors are of the D2 and D3 sub-type and we moved on to serotonin and acetylcholine, which also possessed presynaptic modulation of release. The receptors were specific 5-HT_{1D} for serotonin and M2 for acetylcholine. These were called auto-receptors because they were activated by the transmitter released from the same neuron. In other words, the transmitter release was not acting only presynaptically on specific receptors to activate or inhibit the postsynaptic neuron, but it was acting also presynaptically to modulate the release of the transmitter according to the information generated in the synaptic cleft by the concentration of the released transmitter.

WB: So, it set up a model paradigm for the whole field.

SL: Exactly. Subsequently, it was discovered that GABA and glutamate have also presynaptic, receptor-mediated control of transmitter release. Therefore, it appeared that presynaptic modulation of transmitter release is a general phenomenon whereby nature possesses a regulatory mechanism for fine tuning the release of most transmitters, mediated through presynaptic receptors. Of course, the presynaptic receptors are different from the receptors located postsynaptically and this offered new opportunities for drug discovery.

WB: The physiological knowledge about chemicals led to the discovery of drugs. What were some of the drugs you discovered and worked on?

SL: In France, during the 23 years I spent at Synthelabo, the drugs that reached the market are the important ones; many compounds advanced only part of the way and then were abandoned for different reasons.

WB: Yes.

SL: But, I would like to single out aripiprazole, which is an antipsychotic because it has a partial agonist effect on the presynaptic dopamine autoreceptor. Of course, this is not the only effect of aripiprazole because it blocks postsynaptic dopamine receptors and it acts on 5-HT receptor subtypes as well. The advantage of aripiprazole is that it does not increase plasma prolactin, because it is a partial agonist on presynaptic dopamine autoreceptors, while prolactin levels are substantially increased with most anti-psychotic drugs. Another example is mirtazepine, an antidepressant that blocks adrenergic alpha-2 receptors in the central nervous system and that increases the release of norepinephrine. It is also known to increase serotonin release, because serotonin nerve terminals possess alpha-2 receptors that inhibit serotonin release and when you block them with mirtazepine the release of serotonin is enhanced. Therefore, blocking alpha-2 adrenoceptors in the CNS increases both norepinephrine and serotonin concentrations in the brain, and it is widely accepted that in depression, there is a deficit in both noradrenergic and serotonergic transmission.

Another example, to stay with drugs that reached the market, involves compounds for the treatment of migraine. These are sumatriptan and its analogs that are effective because they stimulate 5-HT_{1D} receptors, located presynaptically; when stimulated by agonists it inhibits the release of substance P and Calcitonin Gene-Related Peptide (CGRP), which are important in inflammation and pain. Of course, sumatriptan and its analogs also stimulate 5-HT_{1D} receptors in

vascular smooth muscle and so both presynaptic and postsynaptic components contribute to the anti-migraine effect of these drugs which are used extensively.

WB: So, your preclinical work on presynaptic receptor had a broad effect, but also a major impact on the whole field of partial agonists and on the modulation of other neurotransmitters.

SL: Yes.

WB: What was your specific role in some of the drugs that reached the market?

SL: In some cases I was involved as a consultant in the drug discovery projects. In other cases, these events developed spontaneously in competitive pharmaceutical industries because the existing publications pointed to opportunities in drug discovery.

WB: Based on your pre-clinical work?

SL: Based on information that was published, and because it seemed reasonable to assume that such strategies would yield novel compounds with useful therapeutic properties, and hopefully, with fewer side effects because the pharmacological responses of pre-synaptic drugs are gradual and moderate, while an effect originating post-synaptically may be of greater biological significance. Although, this is a speculative statement, it is likely that side effects of presynaptically acting drugs may be fewer or less severe than those from drugs acting at the level of the classical postsynaptic receptors.

WB: In your basic, pre-clinical work, were there novel technologies you developed necessary to do the work you describe?

SL: The technology of transmitter release from peripheral organs was quite straightforward and almost classic, particularly, transmitter release from the perfused spleen and the heart. I developed special techniques for the cat's nictitating membrane, which required innovation, and it became a very useful preparation. In the CNS, you have to work with slices of different brain regions, all with presynaptic receptor modulation of transmitter release, so you have to choose the areas of the brain rich in the transmitter you are targeting; in the striatum or putamen for dopamine; the occipital cortex for norepinephrine; and the frontal cortex for serotonin. It all boils down to having a very richly innervated area of the brain as a model. But, then, you have to compare your findings to other areas of the brain and make sure that the interaction you are describing is present in areas relevant to a particular disease and to drug therapy. So, it requires patient work that involves several brain regions.

WB: If you had to list your major discoveries what would they be?

SL: I would definitely single out the discovery of presynaptic receptors. We made our first report in the early 1970s and then the subclassification of the alpha receptors into alpha-1 and alpha-2 subtypes, in 1974. In 1976, the concept of co-transmission, namely, that one neuron may release more than one transmitter. That was done in 1976, and carefully demonstrated with both in vitro and in vivo physiological and pharmacological methodology for ATP and norepinephrine. The concept of co-transmission has grown and it does, indeed, exist in the central nervous system, in addition to the periphery. We still need to learn more about it, but it is relevant to the regulation of neurons and their communication with each other by more than one transmitter. There is always a main transmitter and the secondary co-transmitter may have an effect only at certain frequencies of nerve stimulation.

WB: Who else was in your field making major contributions?

SL: In the area of co-transmission, it is essential to mention Geoffrey Burnstock from University College in England, who, at the same time, proposed the concept of co-transmission in a highly quoted article in 1976. In presynaptic receptors, I would like to mention Klaus Starke from Germany, who not only started publishing on the subject in the early 1970s but continued working for three decades on presynaptic receptors in the peripheral and in the central nervous system. As far as receptor subtypes are concerned, the finding of subclasses of alpha-1 and alpha-2 adrenoreceptors I reported in 1974, was important because it happened at the time when alpha adrenergic receptors were universally believed to be of a single category. This finding triggered interest in exploring subclasses and subtypes in other receptor systems. This was long before the development of molecular biology and the possibility to clone and express receptor subtypes and carefully characterize many of them, which offered new targets for original drug discovery by finding selective agonists, partial agonists or antagonists.

WB: It is hard to estimate how many years it will take to look for drugs that have specific receptor subtype action.

SL: Absolutely. This became, in most rational drug discovery strategies, a powerful tool and remains very important approach.

WB: How did you balance your research, administration and industry consultations with your other activities?

SL: It is very time consuming to have the number one responsibility for research and development for a large pharmaceutical firm, which was Synthelabo in France. Today, it is Sanofi-Aventis,

number three worldwide, even bigger now because of different mergers since I left in 1999. There are administrative duties, there are political issues and there is the science. And, unless you leave the top priority for science, you risk getting involved in and paralyzed by administration and politics. The only way for me to survive was to make science a total priority, to stay very close to the lab and to minimize or delegate other activities to allow for the survival of creative research.

WB: I see.

SL: Even minimizing administration it is almost an impossible task to stay up to date with everything that happens in science and navigate towards originality and innovations that address unmet medical needs. For instance, in depression, there are two unmet medical needs. One is the latency period, which is three to four weeks before the improvement in clinical depression is significant, while side effects appear within 24 hours of drug administration. Shortening the latency period may keep researchers and psychiatrists interested in drug discovery. The other issue in depression is drug-resistance; although we have drugs that are superior to placebo, there are still about 40% of non-responders to the first antidepressant. When you have a non-responder after four to six weeks of treatment, you have a difficult problem; to decide on adding a second drug or replacing the first drug and waiting again.

WB: Tell me more about your experience with industry.

SL: I was fortunate and very successful, and that is why I stayed 23 years with the same company.

WB: You had an important position.

SL: Yes, I was fortunate because when I joined Synthelabo in 1977, they were small, number 81 worldwide, but very keen on growing and developing into an internationally competitive pharmaceutical company. Today Sanofi-Aventis is number three, worldwide.

WB: What was your position?

SL: I was Director of Biology when I joined and ended up as President of Research and Development.

WB: This covered all fields?

SL: Including chemistry, biology, toxicology and clinical pharmacology.

WB: So, this involved very heavy administrative responsibility?

SL: Yes, but I delegated by choosing people whom I could trust and were competent. But you cannot delegate too much and so there is a degree of pressure. During this period, I had the freedom to recruit, expand and take decisions that made the company competitive internationally and five

drugs were discovered, developed and marketed. Today, they are best sellers like zolpidem, which is a sleep inducer called Ambien in the USA, to only mention one. It is the best-selling hypnotic drug, worldwide. In Europe it is called Stilnox.

WB: Two major compounds.

SL: One compound; Zolpidem, with two commercial names; Ambien and Stilnox.

WB: They are still used today?

SL: Yes, and this is true for other drugs from this period. So, I must say, that this was a highly stimulating experience. The many years I spent in universities before joining industry were useful to the extent that I developed and worked on research projects relevant to transmitters, receptors and receptor subtypes that offered appropriate targets for novel drug discovery. Working in industry provided an opportunity to add a strong input from medicinal chemistry and the necessary organization to develop and advance candidate compounds which was very fulfilling.

Since I retired from that position, I have two small companies that synthesize compounds in projects of drug discovery for the central nervous system; they are in the early stage, mainly in medicinal chemistry and preclinical evaluation.

WB: Tell us about those two companies.

SL: One is based in Stockholm with the Karolinska Institute and we have a patent on the use of the central α -2 receptor antagonist idazoxan for treatment of drug resistant depression, particularly non-responders to serotonin uptake inhibitors.

WB: In what Phase of development is that?

SL: Phase II, clinical studies; at the level of proving its efficacy in non-responders to serotonin uptake inhibitors.

WB: What is the name of this company?

SL: Alpha 2 Pharmaceutica AB. AB stands for a registered company in Sweden. The second company is based in Tel Aviv and also linked to drug discovery in the central nervous system. We have two projects, one on antidepressants and the second on sleep inducers with the aim of discovering the successor to Zolpidem, which has been a great success but its patent life ended two years ago, so it has been replaced with slow release Zolpidem. Considering the success of Zolpidem, there is still room for improvement with a similar compound in the treatment of insomnia.

WB: Where are those two new drugs at this point?

SL: Still at the preclinical level. We are not even sure whether we have chosen the best candidate, so we are still synthesizing analogs in those chemical series.

WB: How do you manage these two companies? You also have a place in London, as I remember?

SL: We live half in London and the other half in Tel Aviv, which allows me to be in close touch with the scientists who work in the Israeli company, Euthymia, Ltd. In Sweden, my partner is also a member of the ACNP, Torgny Svensson, professor of Pharmacology at the Karolinska.

WB: You've known him for many years?

SL: Yes, many, many years.

WB: When did you become a member of the ACNP?

SL: In 1984.

WB: Who were the key people in the ACNP at the time you joined?

SL: One is talking to me right now and another was Solomon Snyder, for whom I have a lot of admiration. Of course, Menek Goldstein, who I knew for many years but unfortunately, is no longer with us, and Arvid Carlsson, who has been an inspiration for my work in this field and to whom I feel indebted for advice throughout those many years.

WB: I think he has a company also in this area.

SL: Yes, but for dopamine.

WB: But, the concept is similar?

SL: Presynaptic modulation. Arvid is very supportive and has always recognized the significance of my discovery of presynaptic receptors.

WB: Why were these people key for you?

SL: They were inspirational because of their creative research. Also, I was coming every year to the ACNP meetings, which were stimulating and motivational events, because they allowed me to listen to excellent science and to present as well. Also, to discuss informally, with plenty of time, many issues relevant to ongoing research and future projects.

WB: Were you ever on any ACNP committees?

SL: As I was a foreign member, I wasn't involved in committees.

WB: Was there any impact of ACNP on your work?

SL: I presented my work at the ACNP on several occasions and one was the first Earl Usdin memorial lecture many years ago.

WB: I recruited him to Irvine before he died, for about 5 years. Are you happy with the way things have turned out for you?

SL: Yes, I am. First of all, I was lucky to have chosen promising and interesting problems in my research and to have benefited from excellent guidance and mentors in my career, including the privilege of working with Ulli Trendelenburg at Harvard and Marthe Vogt in Cambridge.

WB: It's not by chance you picked those people.

SL: When I was with the Rockefeller Foundation, they sent me to visit Yale and Harvard and both accepted me, so I had to make a choice and it ended up being Harvard, but Yale would have been superb as well. I had access to great places for training, experience and guidance, which had a tremendous impact on the rest of my career.

WB: Where do you think things are going in the next five years?

SL: I could make predictions and probably be wrong, because it is very hard to predict the future; however, I think there are a number of psychiatric diseases where improvement of existing therapy is desirable and possible. I have mentioned two unmet needs in depression and I think progress may be made in the coming 5 to 10 years. Regarding difficulties in clinical responsiveness to the cognitive deficit and the negative aspects of schizophrenia, new antipsychotics may improve efficacy. Neurological and psychiatric diseases are likely to benefit from novel therapies but it is difficult to reverse the process of neurological degenerative diseases, although it is not impossible, and it would represent a major breakthrough if in Parkinson's and Alzheimer's disease it became possible to reduce the progress of the diseases. Of course, that is a very tall order and it may take a long time. Also, genetics is having an impact on neurobiology and although this is not reflected yet in specific gene therapy, that time will come and it may be sooner than expected.

WB: Are there any other areas you would like to cover that I haven't asked about?

SL: It only remains to add among the people from the ACNP that were influential in my career, George Aghajanian, from very early on, was interested in my work and he, himself, characterized the somatodendritic autoreceptors pharmacologically in the mid 1970s; it is always a source of stimulation and motivation to discuss science with him.

WB: Any other things you want to comment on?

SL: I would like to say in closing that although there are areas in drug discovery that could be improved, drug discovery is becoming a very expensive because of the technology, and because there is no place for "me too" drugs, so the only type of medication to incorporate into the market

is a new drug that is effective for unmet medical needs or has superiority over available drugs in treatment of a disease. Therefore, although the price of drugs may be a very sensitive issue, drug discovery would benefit from a longer patent life to provide an enhanced return on investment in research, without punishing the public that has to buy these drugs at the pharmacy.

I'm not against generics, but innovation and drug discovery need to be supported and encouraged.

WB: I find that a very interesting suggestion. I've been interviewing Dr. Sal Langer, one of the giants in neuropsychopharmacology, and I'd like to thank you very much.

SL: Thank you very much for your time, your dedication and our long lasting friendship, which I appreciate very much.

WB: I enjoy very much our friendship, too.

8. HEINZ E. LEHMANN

WB: I'm William Bunney, Professor of Psychiatry and Human Behavior, University of California, Irvine, and I will be interviewing Dr. Heinz Lehmann,* Professor Emeritus of Psychiatry, McGill University, Montreal and Deputy Commissioner for Research for the Office of Mental Health in the State of New York. We're going to go through a series of question about Dr. Lehmann's career and I wonder if you'd start by telling us a little bit about your training.

HL: My training was in Germany. I went to school there, the Gymnasium, and then to some various universities as it was the fashion then in Germany. You went to as many universities for your medical study as your father could afford to send you, so I studied in Freiburg; I studied in Marburg; I studied in Freiburg again, then in Vienna, and finally graduated from Berlin University. But it didn't go that easily, because when I was about twelve, I felt what I can now diagnose as depression, which lasted for almost a year. In those days, children didn't have depression, so that wasn't diagnosed and nobody knew what to do about it, and my main symptom was that I couldn't work. I couldn't concentrate at all, and I couldn't do any homework. Now, when you're twelve years old and in the Gymnasium and you're supposed to learn Greek and Latin and mathematics, that didn't go very well. So, my teachers told my parents that they had to take me out, that I just would never be able to get through high school and I just wasn't made for it and I should learn a trade. Well, my mother didn't believe it and used her good judgment and got me a tutor. The tutor came every day. He was a student, and he did my homework with me, and much of the time for me, actually. He was interested in psychology and he saw that obviously I couldn't do it; I couldn't concentrate, so he would do the homework for me. That went on for about six months and I got out of my depression. And so, I did get through the Gymnasium. I got through the universities, and then I had to leave Germany in the late 1930s, because of Hitler, and came to Montreal, Canada. I worked in a mental hospital there, the Douglas Hospital, then, called Verdun Protestant Hospital, and I didn't have the time to get any postgraduate training. I've always been interested in

* Heinz E. Lehmann was born July 17, 1911 in Berlin, Germany. He was educated at the University of Freiburg, the University of Marburg, the University of Vienna, and received his medical degree from the University of Berlin. He immigrated to Canada in 1937. In 1947, he was appointed the Clinical Director of Montreal's Douglas Hospital. From 1971 to 1975, he was the Chair of the Department of Psychiatry of McGill University, Montreal, Quebec. He subsequently served as Deputy Commissioner for Research for the Office of Mental Health in the State of New York. He died on April 7, 1999. He was interviewed at San Juan, Puerto Rico on December 12, 1994.

psychiatry. In fact, before I started medicine at the university, I told my father who was a surgeon that I would become a psychiatrist. Now, back in the early 1930s that was certainly something you didn't go into. There was practically no really good diagnosis, except Kraepelinian. The only therapy was psychoanalysis. But, anyway, I insisted on it, probably because I had gotten through the depression, and my tutor, who got me out of the depression and did my homework with me, was interested in psychology as a student, and he had given me all of Freud's works that had been written until then, all of which I read. By the time I was fourteen, I had read all of Freud's work. That got me interested in psychiatry before I started medicine, and I stuck with it. Everybody said, "You will change your mind about that," but I didn't. But then I didn't have any postgraduate training in psychiatry. There was no time for it. The War started when I started working in the hospital in Montreal, in the mental hospital, and there weren't many people left. I was one of the few, so I didn't have time and I didn't have the money for postgraduate training, so I never got any. I didn't get certified, and later, when this came up, I said, "Well, I certainly didn't have the time to go for the examinations now, and anyway, I wasn't so sure that the examiners would know more than I would, so I didn't bother." Eventually, they sent it to me by mail, the certification, I didn't even ask for it. So now, I'm a certified psychiatrist, without any postgraduate training. Well, what was the training? I learned it the right way, I think, by just working from 8:30 in the morning until about 12:30 at night. I had up to six hundred patients during the War, and there were only two or three doctors left in the hospital. We didn't have interns; we didn't have residents. I had one trained nurse. The others were untrained attendants, and up to six hundred patients. So I did learn a lot, because I spent my time with the patients.

WB: You taught yourself.

HL: I taught myself, and the patients taught me.

WB: Did you read during that time, too?

HL: Yes, I did read. That's what I did after 11:00 o'clock at night or 10:00 o'clock at night in the hospital library. I courted my wife, who was a nurse there, and word got around to her that I probably was a heroin addict, because nobody else would walk around the hospital library at 3:00 o'clock in the morning. So, I did read a lot, and I saw a lot of patients and I learned quite a bit, of course. I was convinced that there was quite a bit of difference between what we then called neuroses and psychoses, and I was convinced that psychoses, such as schizophrenia and the

affective disorders, had some sort of a very strong physical component, and that wasn't necessarily so for the neuroses.

WB: How did the whole area of drugs come up? How did you get involved?

HL: Because I was convinced that there was a physical substrate for the psychoses, so I tried very large doses of caffeine. I came up with the notion that manic depressive swings may have something to do with acidity and alkalinity and pH, so I gave my patients very large doses of ammonium sulfate or sodium carbonate, in order to alter their pH. I was always hoping and dreaming about some drug that eventually would do something to psychosis. Well, then what happened is, that in 1953 – my wife is French Canadian, so we speak French at home – I read a French article by Delay and Deniker on chlorpromazine, on their first experience with chlorpromazine in 1952, and that intrigued me very much. I couldn't believe that psychotic symptoms such as hallucinations and delusions could be affected by a simple pill. But, anyway, I tried it. Of course by the late 1930s, early 1940s, we already had shock treatments. I had been treating patients with insulin coma therapy, hypoglycemic coma, and with Metrazol (pentylenetetrazol) therapy before we had electroconvulsive therapy, and these treatments worked fine for a few weeks or a few months. But then, of course, the patients relapsed, as we know now, about seventy percent of them, and then we didn't know what to do. We applied the same shock treatments again, and the second time they usually didn't work as well.

WB: Didn't you have a role in the first use of chlorpromazine?

HL: In 1953, I read about this pill, and, so, we got samples from Rhône-Poulenc, who made the chlorpromazine. I read the articles one Sunday, I remember, and the next day, Monday, the first resident I met – by that time, in the 1950s, we did have residents – I asked, "Do you want to try this fancy new drug? It seems to be incredible, what they claim for it." And he said yes, so we set up a clinical trial in, I think, seventy-two patients. We got it all arranged in about a week or two, because we didn't need any permission. I didn't even ask the director of the hospital. Certainly, there were no

WB: No Institutional Review Boards (IRBs).

HL: No IRBs, no informed consents, no Food and Drug Administration (FDA) regulations, nothing; also no money, whatsoever. So we had to kind of fold these seventy-two patients into our regular routine. I didn't even have the heart to ask the hospital for a secretary. So, I made my own cards out for each patient. Well, it worked remarkably well, because after two weeks, two or three

of my acute schizophrenic patients were practically symptom-free, and that, I'd never seen or heard about before.

WB: That had to be an exciting week.

HL: Oh, yes. We started our study in May, and in August, we had finished, simultaneously, all seventy-two patients, and we had written the paper. I remember writing in the paper that these were the drug's 'unique effects,' and my boss, another psychiatrist, said in a short note in the manuscript, "don't ever say anything is unique," nothing is unique. But this one was and I insisted on keeping it. At the time, of course, there was no other way to describe it. At first, so, my co-worker and I thought that what we saw was a fluke, and perhaps some sort of mistake.

WB: Who else in the field was studying chlorpromazine at that point in time?

HL: Well, there was Nate Kline. He had started reserpine, which didn't last very long, but it also was an antipsychotic drug. And then I remember Frank Ayd, and I think, Douglas Goldman. I don't think anyone in Canada had worked on it.

WB: Did Fritz Freyhan study it, did he?

HL: Fritz Freyhan, of course. Now, Fritz Freyhan coined the term target symptoms, and that's fine. We did have target symptoms, typical psychotic symptoms like delusions, hallucinations, formal thought disorder. I think for a while, he thought, like many others, that the drugs were anti-schizophrenic, but from the beginning that seemed to be very unlikely, almost impossible. But, we did find that it worked in psychotic manics, even in psychotic depressed patients, as well as in schizophrenics.

WB: You found that out fairly early.

HL: In our first seventy-two patients, we had about twelve different illnesses; a few manic patients where it worked miraculously well, of course, and a few depressed patients, and even a few organic psychoses, where it didn't work very well.

WB: So you had the whole story in those seventy-two patients, almost?

HL: Almost.

WB: In the first paper?

HL: Yes, and then in the next two or three months, before Christmas of that year, we tried it in a few anxious patients, and found out that definitely the drug wasn't an anxiolytic, so we really had the whole story.

WB: Now, in Europe, who was working with the drug at that point?

HL: In Europe, they worked with it primarily in France.

WB: The French, primarily?

HL: Delay, Deniker, and two or three others. Deniker came over to Montreal to visit us from Paris, and we had some jaundice cases, which the French hadn't seen. I haven't seen them since either. Possibly it was sub-clinical hepatitis. From then on, of course, there has been a never-ending chain of new drugs, such as Stelazine (trifluoperazine)

WB: What hospital were you in when you did the seventy-two cases?

HL: The same hospital I'm still teaching in. It was the Douglas Hospital; then, it was called the Verdun Protestant Hospital. I'm still teaching students there every Monday, so that's quite a long time. They have now a research center there. At the time, it was one of those big, well, snake pits, really. It's very nice to see what, over a lifetime, can happen with a snake pit becoming a good research center. Well, that is how I got into psychopharmacology, but really it was realizing a dream. I had hoped there would be a drug for those patients. I'd been looking for it, hoping to find it eventually. From then on, Tom Ban joined me. He had just come from Hungary and for the next ten or fifteen years, we did a lot of clinical trials. There's hardly any drug between 1952 and 1970 that we didn't do clinical trials with.

WB: Well, tell me some of the most interesting findings in those clinical trials.

HL: Of course, nothing can match the unbelievable thing that there was a drug, chlorpromazine, first time in history, that could in two weeks wipe out hallucinations and delusions. After we had really believed that was so, which took a year or so or more, nothing else could really....

WB: Anti-climactic.

HL: Everything else was anti-climactic, yes. But, then, I remember a funny story. I went in 1957 to Zurich to the international psychiatric meeting, and there, on the way back from Zurich to Montreal on the plane, I read Kuhn's first paper on imipramine, which he had given at the meeting in Zurich. I wasn't there; apparently he had about only twelve people in the audience. I read the paper he had written in German, on the way back that there is possibly now a drug for depression. I immediately called Geigy, when I arrived in Montreal, and their branch in Montreal hadn't heard of this; although their company had worked with it, obviously, for more than a year. Well, they felt a little embarrassed, but got me the drug from Europe, and then, we did one of the first trials with imipramine in Canada, and probably North America, and found that it worked, too. But that wasn't so surprising. I had told the various drug representatives, after we had antipsychotics, it

shouldn't be so difficult to find an antidepressant, because it's likely that there's a metabolic disturbance in affective disorder as in schizophrenia.

WB: Do you think we're going to find drugs for the twenty to thirty percent schizophrenics and twenty percent or fifteen percent depressed patients that don't respond to anything; do you think we're going to find a drug for them?

HL: I think so, not one drug, but probably a half dozen, and we'll learn how to make diagnoses based on the substrates involved in depression and schizophrenia, probably. That's where the new imaging technology will help us, probably. So far, we can't make any diagnosis with it, but we may be able to distinguish substrates. So far, all our diagnoses are based on phenomenology, just the way Kraepelin did it, but we will probably be able to find certain traits with endocrinological measures, molecular research or functional imaging that will allow us to make distinctions between various depressives and various schizophrenics.

WB: Do you remember where your first paper on Thorazine was published?

HL: It was in the *Archives*, the *Archives of Neurology and Psychiatry*. It wasn't easy to get it published. We sent it in August and since I hadn't heard anything by December, it seemed that something was fishy. So I wrote them that I wanted the paper back, and "I'll get it to somewhere else." Then, they immediately published it. It came out in March of the next year. I think what happened is that we were in Canada, and the Americans that were working with it, I think Winkelman, wanted to be the first one out. His paper came a month later. He had worked with chlorpromazine in neurotic patients.

WB: The usual story.

HL: Yes.

WB: Who was the editor of the *Archives* then? Do you remember?

HL: No, that, I don't remember.

WB: Was it Grinker?

HL: No, it wasn't him.

WB: It was before him?

HL: It was before Grinker.

WB: Well, you've worked on a lot of different hypotheses and tested a lot of different drugs and had a lot of different theories. Are there any that particularly come to your mind?

HL: No, what I would like now is to find methods to determine sub-clinical minor stress. I'm thinking of that, particularly, because I have a notion that many aging people suffer from subclinical – to them probably unknown – chronic stress that actually kills their hippocampal cells. I think Ewing has shown this, and several others have shown it too. In California, there's a group showing that corticosteroids produce atrophy of hippocampal cells, and a chronic stress condition would of course produce a chronic outflow of corticosteroids. I think a lot of elderly people suffer from chronic stress conditions without knowing it. Now, if we could, well, test for instance, their saliva for corticosteroids, their electrolytes for corticosteroid receptors, we would possibly be capable of finding in a lot of people, who would never know about it, and the doctors don't know about it, that they are chronically stressed. If they are chronically stressed, then one would have to find out why, and probably with psychotherapy; they could be helped to get over this change in their lifestyle, or whatever it is. There's a lot of undiscovered chronic stress. Some people have suggested that post-traumatic stress might be due to an outflow of corticosteroids.

WB: Going back to your first major study with chlorpromazine, did you present it at a meeting before it was published? Do you remember?

HL: No, I didn't. I presented it a year later at the American Psychiatric annual meeting.

WB: After it was published?

HL: After it was published. And I was very much surprised when people clapped and applauded when I went up to the podium. I never expected it, and didn't know why and that was the first time....

WB: That was the first time you presented it?

HL: That I presented it.

WB: And, they, obviously, knew about it?

HL: They knew, because they read the paper.

WB: Right, right.

HL: But, I didn't realize that it had caused the impact.

WB: You didn't know the impact.

HL: I didn't know the impact.

WB: What do you think was the biggest contribution that you've made?

HL: To psychiatry?

WB: Psychiatry.

HL: Psychiatry needed a big contribution to show that the psychoanalysts were wrong. Up to the early 1950s, the teaching in most American universities was that it is simplistic to believe that there's any kind of organic substrate to schizophrenia; that most psychoses, except the organic ones, could only be treated with psychoanalysis and that any other treatment than psychoanalysis was anachronistic and just simplistic. We had to show that there was a physical cause, a physical substrate, physical pathophysiology for the major mental disorders. And the only way to show this, and therefore, to help patients to get the right kind of integrated treatment, was by proving that with a pill you could remove hallucinations. Having shown that, the analysts had to admit that there was a physical cause, and we could begin to use the biopsychosocial model that we have now. I think that was the main contribution I made.

WB: Just go to the various positions you've had.

HL: Well, as a refugee from Germany and untrained psychiatrist; I was a Junior Psychiatrist at the Verdun Protestant Hospital, the hospital I'm still working at once a week, and then I became Senior Psychiatrist there, then Clinical Director, and I stayed there for thirty-five years, full time. Incidentally, I don't know any other psychiatrists who stayed that long, full time, with a mental hospital, so I think I have credibility in knowing my schizophrenic patients. I became Director of Research and Education at that hospital, and then I became Chairman of Psychiatry at McGill University. I didn't want to, because I didn't want to have anything to do with administration. I hated anything that had to do with administration. I thought it was just a waste of time; so when they asked me whether I would take the chairmanship, which was open, I still remember, I told the dean I needed it like a hole in my head. Well, he didn't like that, so he insisted then, and finally, eventually, I took it on. I took it on because the department was almost falling apart at that time. That was in 1970, at the time of the Quiet Revolution in Quebec. There was a lot of unrest and a lot of psychiatrists and university teachers were leaving, so I thought, well, I'd better take it over, because I was from there and I knew about holding things together, anyway. So I took on the chairmanship. Then later, after I had finally left the full time hospital job, I took on, originally for about a year, the job that I still have now, since 1980, as Deputy Commissioner for Research for the New York State Office of Mental Health. I have no license in the state, so obviously, I'm not practicing there. It's all administration, the one thing that I've hated all my life and kept away from, but I thought, well, at that age, then, after sixty-five, it was about time to learn a little about it, and so, that's when I came on.

WB: What does that involve?

HL: Well, I have a budget of some thirty-six or thirty-seven million dollars a year on paper, but it actually involves being responsible for the administration of two major research institutes, one of which happens to be the Nathan Kline Institute, and actually, for all the research that is going on in the state of New York. I have to sign off on all of the research protocols. I have to make sure that every IRB is working all right. I have to deal with all the political inside fighting about the various jobs in the various hospitals and research institutes. I have to fight about budgets and try to outwit people, get around and manipulate; you know, I do the things that administrators have to do. But, since I'm there only two days a week in Albany, and I live in Montreal, I live, really, in two worlds. The Canadian world is very different. I don't know what the Americans are going to do with their healthcare, but in Canada, of course, there's no problem. But it's interesting to have a position that all my life I never dreamt about, and in another country, in another political world, altogether.

WB: And it's a very responsible position.

HL: It's a very responsible position. Well, I had the experience, obviously. It's interesting, I think, that I know more researchers in the States than in Canada. Some of the Americans took quicker to developments, and I was more in communication with American researchers than with Canadian researchers.

WB: Let me ask you, since this is the ACNP, what was your involvement in the beginning with the ACNP? You were one of the founding members.

HL: Yes, again, against my wishes. I remember quite a few of the people that I knew quite well asked me to join them in founding the ACNP, the American College, and we had had meetings, and I said, "well, that's fine, but leave me out of it." I said, "I had no time, definitely no time, and I hate institutions, anyway, and I don't want to have anything to do with it." Then, I think it was Malitz who told me, "Well, we'll draft you," and I said, "I don't know what you mean." He said, "You don't know what drafting is?" So he explained to me what drafting is, and so anyway, they got me into it, and, I finally became one of the founders. Eventually, they drafted me again for being a president. I think it was in 1964. Again, I didn't want to, and I said, "I don't know anything about the procedures of running it." Anyway, I got into it, and as I was doing it, I was learning it. Now, I'm very glad that we have an ACNP. In fact, it's very difficult to imagine that we didn't at any time.

WB: Looking back on your life, were there key turning points?

HL: No, really not, except that I had to leave Germany, which I didn't like at the time. I made one big decision within the first three weeks after arriving here, never to have a car. I kept this promise to myself. I think that helped me; otherwise I wouldn't be alive anymore. I was driving in Germany as a student. Otherwise, my life has become, really, remarkably the way I wanted it to go, step by step by step, no great crises, no great surprises. One of the surprises was chlorpromazine, but that wasn't such a surprise. My father, as a surgeon, told me "it's ridiculous to want to go into psychiatry," which was ridiculous at the time. I thought, well, perhaps I can do something about it if he knows so little about it. So, you know, that wasn't planned.

WB: Okay, well, maybe one last question: as you look to the future, now, of our field, what do you see as the challenges?

HL: After we had the serendipitous discovery of the drugs for the affective disorders and for the psychoses, we didn't know what they were, so we challenged the neuroscientists: "Now, you've got to find out why the antipsychotics work, why the antidepressants work." They found out first why the antidepressants work, and another five years later, why the antipsychotics work, and, from then on, neuroscience took off. Before that, we had a lot of anatomy but we did not learn very much more about what goes on in the brain. And now, neuroscientists are far ahead. We clinicians set them going, and they are very successful; they have left us behind. I don't think we have enough communication, and perhaps the focus isn't right. It's difficult for me to see the focus of the neuroscientists and molecular biologists. Well, there is a C-fos and N-RAS, and that works on a receptor on the cell wall, which then enables certain chemicals to get into the cell, which enables something else to help in the cell. You don't even have an aggregate of neurons anymore. It's all within one cell and, from the neurons to the brain and from the brain to the behavior and from the behavior to the human being, there's a gap.

WB: The gaps.

HL: Huge gaps, so we have to find a way to communicate and to get a general focus, which is the same for research and clinicians.

WB: Okay. I've been interviewing Heinz Lehmann, who has been and is one of the pioneers in the field of neuropsychopharmacology. He's past president of the American College of Neuropsychopharmacology, and clearly, one of the greatest neuropsychopharmacologists that ever lived. I enjoyed interviewing you.

HL: Thank you. I think you exaggerated a little.

WB: No, I'm not exaggerating. Are there any other things you'd like to add? We can always go back and dub it in if you want.

HL: No, I also want to make the point of having had this long-lasting depression which was so disabling at twelve years of age that the experts said that I would never make it. I got over it and have been doing fairly well for quite a long time without any drug therapy or any definite structured psychotherapy.

WB: Have you had subsequents?

HL: Subclinical ones.

WB: Subclinical ones?

HL: I had one or two, that's all. I never had to stop working. Once I took a drug, for a short time. For me that indicates that the prognosis is not as bad as recent follow up studies have shown.

WB: Right. There are many stories of educators who've told people they can't do it, and fortunately, a parent said, "but you can do it" and stuck with it.

HL: And the therapy of my tutor, doing the work for me, the homework, you know, which was considered to be horrible, his bibliotherapy of giving me all of Freud's stuff to read, when I was thirteen, apparently worked.

9. WILLIAM E. BUNNEY, JR. interviewed by Thomas A. Ban

TB: This will be an interview with Dr. William Bunney[□] for ACNP's Archives of Neuropsychopharmacology. We are at the annual meeting of the College, in 2001, in Hawaii.

I'm Thomas Ban. Let us start from the very beginning. Tell us where and when were you born, say something about your early interests, education, professional training, and how did you become involved with neuropsychopharmacology.

WB: I was born on June 27th, 1930, in Boston, Massachusetts. After six months, we moved to East Lansing, Michigan, and after eight years we moved to New Jersey, near Princeton. We stayed there until I went off to college in Oberlin. Then, I went to the University of Pennsylvania Medical School; I took an internship at Henry Ford Hospital, and a residency in psychiatry at Yale. After Yale, I had my first job at the National Institute of Mental Health.

TB: When did you decide about medical school?

WB: Very early in high school, in my sophomore year. I had a really great biology teacher. She asked everyone in the class to do a science project. In reading through our biology book, I noticed that they did not know the digestive enzymes in the earthworm, *lumbricus terrestris*. I thought that would be an exciting topic to study so I bred earthworms, dissected three areas of their digestive system and did crude assays for three enzymes. Prior to doing this, I went to the University Library and read up and talked to a couple of experts in biology about the work I intended to do. I found that in fact, no one did know what digestive enzymes there were in the *lumbricus terrestris*. So, I wrote it up and got an A+ on the project and was hooked on science from then on.

TB: That's great!

WB: So that was the beginning of my interest in science. When I was in college, I wasn't sure whether I wanted to go into psychology, psychiatry, or either. I also went through periods of time when I wanted to be a minister. One summer, I served as a minister for a rural community and that was fun. There were three people and four dogs in my first congregation, and by the time I left,

[□] William E. Bunney, Jr. was born in Boston, Massachusetts, in 1930. He received his M.D. from the University of Pennsylvania and completed his psychiatry residency at Yale. He worked at the National Institutes of Mental Health until he was recruited by the University of California at Irvine to become the Chair of the Psychiatry Department. He was interviewed in Waikoloa Village, Hawaii on December 10, 2001.

two hundred more people had joined. But even though I enjoyed that, I decided very rapidly that I did not want to be a minister. Before finishing college I was pre-med, applied to a couple of medical schools, and got into Cornell University and the University of Pennsylvania. I decided to go the University of Pennsylvania. During medical school, I did some research on the thalamus, none of which was ever published.

TB: Could you tell us something about the research you were doing?

WB: I don't remember the details but it was in anatomy, studying the thalamus in rats. After I finished medical school, I decided I wanted to go into science; so, I went to the National Institute of Health (NIH). My dad had previously hired Jim Shannon, who was then director. He had hired him to head up research for E.R. Squibb & Son, where my dad ended up being Executive Vice President. Jim Shannon headed up their Research Institute and was then recruited from that position to head up the NIH. He was probably one of the most famous scientists to hold that position. My dad got me an appointment with Shannon and I went in to see Jim. I remember it was a hot summer day; Jim was in a totally rumpled seersucker suit and said, "I think you should go back and take your internship, take a residency, and then come back to see me." So I got an internship at Henry Ford Hospital, and about half way through, I began interviewing because I was still interested in psychiatry. I liked it in medical school and in my rotating internship.

TB: Didn't you do your residency at Yale?

WB: I went to Harvard first, was interviewed, but they would have nothing to do with me. So, I went to Yale and they accepted me. But then, I was still interested in many other things.

TB: Like what?

WB: When it came time for me to make a decision on whether or not to accept the Yale appointment, I decided I wasn't going to go; I wrote and told them I was turning it down. I planned to go to Colorado, work in an Emergency Room, ski on the weekends, and finish a novel I was writing. Gene Brody was in charge of Residency at Yale. He wrote me and said, "We've turned down 31 people for this position and if you're not coming, let us know in 24 hours!" I thought it over and figured maybe I could get good material for a novel in a psychiatric residency. So I wrote back and said, "OK, I will come."

TB: What happened to the novel?

WB: I had written half the novel but I never finished it.

TB: Hmm.

WB: After my first day in psychiatric residency, I totally loved it and things moved in a straight line from then on. I came close to not going into psychiatry.

TB: It seems you did. You were interested in writing.

WB: I was; and I ended up doing a lot of writing. I have written over 365 scientific papers and edited seven books. I have also written a lot of poetry.

TB: So you are still writing?

WB: It's on the back burner but someday I will probably do that. All my life, I have written poetry.

TB: OK. So after your first day in residency, you fell in love with psychiatry.

WB: It was love at first sight. I wrote my first paper with Tom Detre, who was at Yale at the time. He was somewhat of a maverick back then; he was saying we should treat patients with drugs when the rest of the discipline was saying we should use psychotherapy and psychoanalysis. I wrote my second paper with Danny Freedman who was also there.

TB: What was the work you wrote up in that first paper?

WB: Tom Detre had developed a vibration machine which we tested. His hypothesis was that sensitivity to vibration was perceived differently by schizophrenic patients. So we did a study where we investigated the responses of normal individuals and the responses of schizophrenics; and, sure enough, the schizophrenic group exhibited a difference in sensitivity to vibration.

TB: Statistically significant?

WB: Yes. We found significant differences.

TB: And that is what you published?

WB: We published the data.

TB: When was this?

WB: Probably in 1959. I remember that because in 1960 I went to NIH.

TB: What about the second paper with Danny Freedman?

WB: We were interested in Rapid Eye Movement (REM) sleep, which was already known at that time. We had one subject we hypnotized, telling her she was watching a ping-pong game.

We wanted to see if we could replicate REM sleep with hypnosis.

TB: Did you do the hypnosis yourself?

WB: I did, but this was a very susceptible person. We analyzed her sleep EEG.

TB: By hand?

WB: It had to be by hand back then.

TB: You talked about Tom Detre and Danny Freedman. Was there any other person at Yale you would like to mention?

WB: Another very influential person at Yale was Jules Coleman, who was a maverick and taught psychotherapy. His was a brilliant psychotherapist and had a cult among the residents. After that I applied to the NIMH and they hired me.

TB: As a resident, what kind of drugs did you use?

WB: We were using reserpine and imipramine. Tom Detre was supportive; everybody else thought he was far out.

TB: What about ECT or insulin?

WB: When I took my psychiatry rotation for a month at Henry Ford Hospital, they were using insulin. Every severely sick patient was treated with insulin coma or ECT. In the course of ECT, some patients were regressed down to diapers and bottles. So, these grown people would be put in diapers and given baby bottles. It was amazing.

TB: So, they did regressive ECT.

WB: I don't think Henry Ford Hospital was very progressive, at the time.

TB: What was your first assignment at NIMH?

WB: I was in Lyman Wynn's branch, in Jim Moss' section, in charge of the depression ward. David Hamburg was branch chief at the time.

TB: Was Joel Elkes there?

WB: Yes, and also Fritz Freyhan, as well as Seymour Kety. Kety and Lyman would argue all the time. Bob Cohen was there; he was the person who did everything. He and John Eberhardt hired everybody, they were a team.

TB: Were your activities connected in any way with the research in Joel Elkes' group?

WB: Totally separate. Joe Elkes was at the St. Elizabeth's Hospital. I went there on occasion, but not more than ten times.

TB: Were you one of the first hired for a new program?

WB: Jack Durrell had one ward and I had another; Jack was a little more senior. He was at Yale with me, and when he came to NIMH, he worked with Kety. He had a biological ward and my ward was transitional, not completely biological.

TB: Didn't you work with David Hamburg?

WB: Dave Hamburg and I wrote a paper about a rating scale that ended up as a citation classic. It also laid out how you develop and run a research ward. So, it was a methodological paper that probably set criteria for developing research wards around the world.

TB: Where did you publish it?

WB: In the Archives.

TB: So, that was an influential paper?

WB: I think it was. After that paper was published, for the next ten years, scientists who wanted to develop a research ward came and visited us.

TB: Could you tell us about the research you were in charge of?

WB: We collected cerebrospinal fluid, urine, and blood samples and analyzed them for corticosteroids and metabolites of the neurotransmitter-related compounds we were interested in. Collection of those samples went on 24-hours a day. We also developed a rating system, in which the nurses rated the patients every hour, 24 hours a day. So, we had behavioral ratings and biological data we could correlate. We developed an informed consent system that was as good as any developed since. The process involved patients in a group meeting, hearing about the procedure before deciding whether to participate. A patient would say, "I'm supposed to have a spinal tap?" and someone in the group would say, "Oh no, don't do that, it was so painful," and three other patients would say, "I didn't even notice it." That was informed consent! Everybody sitting there talking about the process, giving individuals a chance to make up their mind. Most of them went along with it and some of them would say, "No, I don't want to do that." It was totally different than reading a piece of paper and signing your name. That was a long time ago, before anybody even thought about Institutional Review Boards (IRBs) or informed consent forms.

TB: Yours was a depression ward?

WB: We got the most severe depression cases in the entire metropolitan area. These were really sick, very depressed patients, many suicidal. I remember one research subject, a physicist whom we had on constant urine collection. Whenever subjects left the hospital, they would take their

specimen bottles with them. One winter day, this individual went to a bridge of about a 150 feet elevation and jumped into the water. He left his specimen bottle at the point where he jumped; there was a note, "Please return this to Dr. Bunney at the NIH." Fortunately, he was saved because there was a man in a rowboat who saw him jump, got him out of the ice flow and saved his life.

TB: The research was a kind of group activity; everybody participated?

WB: Right, it was a research team, and in particular, the nurses felt they were a part of the team. There was no question about that. They would argue about the ratings and try to get them right.

TB: Were you using your own rating scale?

WB: We used the scale Dave Hamburg and I developed. A lot of researchers used it.

TB: Could you tell us something about your publications in those years?

WB: In one of the papers we reported our findings on urinary 17-hydroxycorticosteroid levels in 90 patients. In 4 patients, who committed suicide or made a very serious attempt, 17hydroxycorticosteroid levels were highly statistically significantly increased. We always said that should be used as a screen when thinking about whether one should discharge or send a patient out on pass. It was a valid test. It was replicated in three or four studies.

TB: Any other publication you would like to mention from that period?

WB: One early publication was the catecholamine hypothesis paper that also became a citation classic. It was written at the same time Joe Schildkraut wrote his catecholamine hypothesis paper; so there were two papers which were somewhat different.

TB: Any other publications?

WB: Another paper we wrote early was a report on a double blind placebo controlled lithium trial, in which we had one patient whom we took off lithium seven times and each time had a striking relapse. The findings of that study had an effect on the whole field. Our paper came out about the same time as Mogen Schou's. It was a product of the research methodology we used; we had ratings every hour every day. We could see patients receiving placebo got worse, and when put back on lithium, they got better within a few days.

TB: Wasn't it one of the first papers on lithium in the United States with favorable findings?

WB: Before my paper, Sam Gershon, and later, Ron Fieve did work on lithium.

TB: Who were your primary collaborators in those years?

WB: Dennis Murphy, Fred Goodwin, and John Davis. I hired all three at NIMH, as clinical associates.

TB: How long did you run the depression unit?

WB: Ten years, maybe. Later, I was in charge of the Biological Psychiatry branch. Chris Gillin worked with me in those years.

TB: Any other research before you became branch chief?

WB: I did some work with Jack Durrell. Keith Brodie, who ended up being President at Duke, was working with me at the time, before he went to Stanford.

TB: What did he do?

WB: Keith participated in many of our research projects. He published a record number of papers for a clinical associate and still may share the record with Dave Kupfer. It was a very productive period in my life time. There were many people working with me in those years. I once put together a list of scientists and there were 72 collaborators over a period of ten years.

TB: 72 people!

WB: There were a lot of clinical associates.

TB: Would you like to mention a few of them by name.

WB: The key ones, Goodwin, Murphy, and Davis I already mentioned. Dave Janowsky was another one who worked with me.

TB: Then you became Section Chief?

WB: I became Section Chief, and then, I was on vacation when I received a call. Burt Brown said I want you to be Director of what became NIDA. I went back, talked with him, and decided to do it. So for three and a half years, I was director of Division of Narcotic Addiction and Drug Abuse, as it was called. During that time, my budget went up from \$44,000,000 to \$240,000,000. I had about one thousand people working for me, including the staff at Lexington. That was my PhD. in administration because I was in charge of education, research, and development of the clinical programs, and of all the international interactions. We funded Sol Snyder when he did his opiate receptor work and I participated in the news conference where he and Candace Pert announced the discovery of the opiate receptor.

TB: Where did you move after NIDA?

WB: I had made an agreement with Burt I would be able to go back to the Institute, if I wished, and he honoured it. Just about the time I went back, Lyman Wynn left the Institute and I took over his Branch. I hired a bunch of basic scientists, including Dorothy Gallagher, John Tallman, and Candace Pert, who did outstanding basic work. I also negotiated so that I could develop a child program and I hired Judy Rapoport. Judy came to head up the child program and did a spectacular job. I had a sleep study program with Chris Gillin and a genetic program with Elliot Gershon. So, we put together a genetic program and Judy put together a child program. We had Will Carpenter on the schizophrenia ward before he went to head up the program at the Maryland Research Institute.

TB: What about Bob Post?

WB: Bob Post was there. When I took the job at NIDA, Dennis Murphy was made a Branch Chief and Fred Goodwin was also made a Branch Chief. Then John Davis went to work with Danny Freedman in Chicago.

TB: As branch chief, you created several programs. Could you tell us something about the research in the different programs?

WB: Looking at dopamine metabolites and schizophrenia was a hot area in those years. There were small drug trials that we did. In depression, we tried cocaine, and we used naloxone to see if we could turn off hallucinations but could not replicate the Scandinavian findings. We did some work on dialysis in schizophrenia, trying to replicate others findings. We published a number of negative papers. We looked at GABA agonists in schizophrenia and they didn't work; that still stands. We gave high-doses of diazepam and that did work in some really sick schizophrenics, but it had side effects that made it unusable.

TB: Then you were promoted?

WB: Yes, I was appointed Deputy Clinical Director under Bob Cohen and during the last period before I left the NIH, I was Acting Scientific Director of the entire Intramural NIMH Program.

TB: Why did you leave NIMH?

WB: I felt I needed a new environment, new stimulation. There were a lot of things going on at that point in my life. UCI made me an outstanding offer, and it had as good neuroscience as almost any place in the world. That was very intriguing.

TB: What year was that?

WB: That was 1982.

TB: So, you moved to California and became chairman of the department of psychiatry at Irvine.

Did you take anyone with you from NIMH?

WB: Earl Usdin and Monte Buchsbaum.

TB: So you had in mind to continue with your work in imaging?

WB: I got a PET scanner within a year and I still I think it is one of the few PET scanners in a department of psychiatry anywhere in the world.

TB: You have been involved very actively in PET scanning for many years.

WB: Yes. Monte Buchsbaum and I had done the first human PET scan work at the NIMH, and when we went to UCI, we continued that.

TB: What was Earl Usdin doing?

WB: Earl was a master at organizing meetings and editing books. Then he got lung cancer and died.

TB: When did this happen?

WB: Very soon after we went to Irvine. And that was very sad. One hundred and fifteen of the top scientists in the world came to show their respect for Earl before he died.

TB: Can you tell us about your activities after your arrival to Irvine?

WB: It was a learning process. In the beginning, I got a MacArthur grant. That was fine, I was not doing a lot of research but running the department and that's a big job. After that, I stopped running the department for a period, and about three years ago, I picked it up again. I didn't have any NIMH funding until about twelve years ago. Then I got a Center Grant with Ted Jones, who is probably the best neuroanatomist in the world today, and we did a series of ten papers together. We started out by collaborating with other brain banks, and then developed our own and Steve Potkin helped. For the last ten years, we have had a brain bank funded by the NIMH. They funded us to do neuroscience research but we also developed the brain bank. The work that came out of that was quite significant. We showed a decrease in GAD 67 mRNA in schizophrenia. As you know, nothing is ever replicated in schizophrenia, but this has been replicated by David Lewis, and subsequently by three other groups. We did a lot of research with the NMDA receptor and also showed that the subplate cells which move from the ventricular zone to just below the cortical plate were maldistributed in schizophrenia. So, something went wrong during the second trimester of development. We don't know what but those cells did not migrate to the correct spot. That was done on our Center grant ten years ago with Ted Jones and Schahram Akbarian.

TB: Did you continue with that research?

WB: We continued, and then, three years ago, applied for a Silvio Conte Center grant and received one. For a Conte Center, you are supposed to put together a group of top people. So I got Huda Akil

and Stan Watson from Michigan, Ted Jones from UC Davis, and David Cox from Stanford. Cox went to the Perlegen Company, so his co-chair, Rick Myers, of the Human Genome Center came on the grant. The research is going on right now and we are two years into a five-year grant. I have been very interested in genetics for the last four years. I am not a geneticist but I decided the only way to learn it was to teach it. So I started teaching a course to residents and faculty. In order to prepare a lecture, you learn a tremendous amount, including a lot of the language. I am very impressed with microarray technology and had a session here on that. I have developed a major microarray facility, and so has Michigan. Our initial study involved five males and five females. People said you can't run microarrays twice in your own lab and get replicable results. But out of 4,600 genes, we were able to come up with six significant genes and five of those were replicated in all three centers. Then we did RT-PCR that validated it. I presented this at a neuroscience meeting and had a poster there; a scientist came up to me and said, "I spent my life working on mice in terms of male-female gene differences and you've come up with the same genes." We were really excited about that and now have a couple of papers we are working on. Just this month, we finished our first cohort of depressed patients and we have some very interesting genes. We have another couple of months to go because we have to put our three groups together, we have to go through the various cluster analyses of these, and we have to figure out what these genes do. That's just for openers, but within another couple of months, we will be able to look at all 40,000 genes on two chips. It is not out there yet, but we spent four hours talking with Steve Fidor, who is president of Affymetrix, and he says they are definitely going to have this technology. So, we will be able to survey 40,000 genes in the future. We've got a second cohort and Blynn Bunney reviewed about six hundred papers to try to figure out which areas of the brain are implicated in depression. From lesion studies, tumour studies, and a large number of brain imaging studies, we came up with twenty-four areas in the brain. We all get together and work around the clock for about 36-hours to dissect these areas out. So we have about six thousand pieces of brain tissue from our cohorts, which are labelled with bar codes and frozen at -80 degrees Fahrenheit. I hired Bill Byerley, an outstanding geneticist. You look at the animal models and see what genes are implicated there. Then you factor in what you understand and know about pathophysiology. I call it quadrangulation of information. We screen and validate with microarrays. Let's say you have eight schizophrenic genes, four of which were in hot spots of the genome, three of which were implicated by a drug model of schizophrenia like PCP and happen to relate to dopamine. It's not going to be that simple but that's the idea.

TB: Sounds like cutting edge science.

WB: It is a very exciting time right now. You could not have done this before the mapping of the human genome plus the development of microarrays. We have a superb team working on this.

TB: You put together a new team and you were able to generate the necessary funds.

WB: The department is doing very well. Every year, the contracts and grants people publish the amount of money all the departments have in terms of research. In terms of total research dollars, our department ranks #1 out of the 23 departments, above medicine. I am very proud of the people in our department.

TB: You should be. Besides all this, you have been involved in all kinds of international activities during the past twenty years. Would you like to talk about that?

WB: I have been interested in international research all my life but it started with the World Health Organization (WHO) group that Norman Sartorius put together. It was a group of collaborative research programs originally involving about eight countries. We would meet once a year and plan programs. We did genetic and clinical studies, as well as biological studies over a period of approximately ten years. It was quite successful, we all contributed funding and everybody worked pro bono. I really enjoyed getting together with everybody. There were scientists from Russia, England, Belgium, India and Morocco. Alec Coppen, Hans Hippus, and Sol Langer were in it. We would rotate and meet in the various countries to plan research programs.

TB: Would you like to mention some of the studies?

WB: There was this color blindness genetic marker we studied. We did a variety of medication studies, published in top journals. It took a lot of effort because you had to standardize everything and to translate everything into the language of the country studies were conducted in. If you had rating scales, they had to be translated, and then you had to get together and test their reliability.

TB: Did all this start in the mid 1970s?

WB: Yes, and it went on through 1984.

TB: Among your different activities, you also served on many advisory boards. Would you talk about your experience?

WB: I served on the Board of the Max-Planck Institute. I have been on NARSAD (National Alliance for Research on Schizophrenia and Depression) from the day they started and that has been an incredible success story. Three weeks ago, I reviewed this year's applications, and there were 500 from Young Investigators. NARSAD is an amazing organization. The Manic Depressive and

Depressive Association has survived lots of problems and is also going strong at this point. I was also on the IBM Medical Advisory Board and the Merck Advisory Board.

TB: What would you consider your single, most important contribution to research?

WB: I would list the lithium studies, the norepinephrine hypothesis, and the one that is in press right now. It is a molecular genetic study in which we have a cohort of fourteen schizophrenic patients, individually matched with controls.

TB: Could you tell us more about this study?

WB: I went a number of years ago to Paul Greengard and said, "Let's look at DARRP 32 in schizophrenic patients." He asked me why, and I said that DARRP 32 is regulated by the two neurotransmitters most implicated in schizophrenia. It is reciprocally regulated with glutamate and dopamine and its downstream effect on protein pump inhibition (PPI) is critical for ion channels, neurotransmitters, and transcription factors. He said, "That's great, I have somebody to work on this." It only took us about eight years to do this study, but it is impressive, and it will be published in *Archives of General Psychiatry*. We found low levels in the dorsal lateral prefrontal cortex and not in other areas and not in other proteins, and they weren't changed by animals chronically on neuroleptics and weren't differentially affected in a couple of patients who were not on neuroleptics. We had a control group of eight Alzheimer's patients, eight on and eight off neuroleptics; there was no difference and they were matched. I think it was a really nice study and took a long time to do.

TB: So, you think these are your three most important contributions?

WB: These were important contributions and I'm sure there are others. Another major contribution is the switch process.

TB: You've received several honors and awards. Would you like to mention a few?

WB: I would say election to the Institute of Medicine-National Academy of Science (IOM/NAS), the Presidency of four organizations; Psychiatric Research; The West Coast College of Biological Psychiatry; The American College of Neuropsychopharmacology (ACNP), and the Collegium Internationale Neuro-Psychopharmacologicum (CINP). The highest honor was certainly the ACNP presidency. I was asked a year ago to be editor of a new neuroscience journal and that is an honor. The most recent award I received was a month ago from NARSAD.

TB: Aren't you a recipient also of the Anna Monika Award?

WB: Yes, I had the Anna Monika Award.

TB: What did you get the Anna Monika Award for?

WB: That was for the write up of the switch process. It was 35 years ago, in the late 1960s.

TB: You are still active.

WB: I have the Della Martin Chair of Psychiatry, but I am Co-chair of the Department of Psychiatry, also. And I also have a Distinguished Professorship at UCI.

TB: Is there anything else you would like to talk about we did not cover?

WB: I don't think so. Science has always been exciting and could not be more exciting than right now.

TB: You mentioned at the beginning that you have always been involved in poetry. Are you still writing poems?

WB: Yes, I still write poems.

TB: Have you ever published any?

WB: No, I've received a lot of rejection slips. At one point in my life, I submitted poems to the New Yorker, New York Times, and Atlantic Monthly. You know, the first time they just send you a stamp informing you that you are rejected. Then, they send you a note saying, "rejected. "And then, they send you a note saying, "Well, we liked this, but we didn't like" I got to the last stage but I never got to the acceptance stage.

TB: We talked about your papers, but we didn't talk about your books.

WB: I have seven edited books. I may have written one or two chapters in them.

TB: Could you tell us something about the books?

WB: A couple of them were on substance abuse. Jack Barchas and I did one for Earl Usdin.

TB: Is there anything that you would like to see happen in the future in psychiatry and in neuropsychopharmacology?

WB: It's too bad that probably only 40 of the 125 departments of psychiatry have science programs. It would be great if there was a granting system to get them started. I think research is so important for the education of young residents. I would like to see distinct mentorships worked out. Residents don't have to become scientists but they should learn to read a science paper and know how to evaluate new treatments, new thoughts about diagnosis; science is the way to learn that. There is currently a lack of clinical researchers, the NIMH is very concerned about this, and I share their

concern. I have been very active with the Institute of Medicine (IOM) and I am currently chairing a committee on suicide, which has been neglected. You have about 5,000 more suicides than homicides in this country, so we are doing a full report on this.

TB: Anything else you would like to add?

WB: I think we've covered a lot. I have enjoyed the interview. I think you have done a superb job, Tom. You are an excellent interviewer.

TB: Thank you. Thank you for sharing all this information with us.

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Levine J, editor. Psychopharmacology. (Volume 4 in Ban TA, series editor. An Oral History of Neuropsychopharmacology. The First Fifty Years. Peer Interviews). Brentwood: American College of Neuropsychopharmacology; 2011.

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Shorter E, editor. Starting Up. (Volume 1 in Ban TA, series editor. An Oral History of Neuropsychopharmacology. The First Fifty Years. Peer Interviews). Brentwood: American College of Neuropsychopharmacology; 2011.

Sulser F, editor. Neuropharmacology. (Volume 3 in Ban TA, series editor. An Oral History of Neuropsychopharmacology. The First Fifty Years. Peer Interviews). Brentwood: American College of Neuropsychopharmacology; 2011.

APPENDIX 1: Curriculum Vitae of WILLIAM E. BUNNEY, JR.

WILLIAM E. BUNNEY, M.D.

CITIZENSHIP: United States **MARITAL STATUS:** Married

EDUCATION

1952 - B.A. (Pre-Med.) Oberlin College, Oberlin, Ohio
 1956 - M.D. University of Pennsylvania Medical School, Philadelphia, Pennsylvania
 1956 - 1957 Internship, Henry Ford Hospital, Detroit, Michigan
 1957 - 1960 Residency in Psychiatry, Yale University
 1965 - 1968 Washington Psychoanalytic Institute
 1966 Training in Radiation Biophysics, NIH

BRIEF CHRONOLOGY OF EMPLOYMENT

1960 - 1962 Clinical Associate (Commissioned Officer), Section on Psychosomatic Medicine, Adult Psychiatry Branch, National Institute of Mental Health (NIMH), Bethesda, Maryland
 1962 - 1966 Project Chief, Studies of Biochemical and Behavioral Factors in Depressive Reactions, Section on Psychosomatic Medicine, Adult Psychiatry Branch, NIMH, Bethesda, Maryland
 1966 - 1968 Chief, Section on Psychosomatic Medicine, Adult Psychiatry Branch, NIMH, Bethesda, Maryland
 1968 - 1971 Chief, Section on Psychiatry, Laboratory of Clinical Science, NIMH
 1971 - 1973 Director, Division of Narcotic Addiction and Drug Abuse, NIMH
 1973 - 1982 Chief, Biological Psychiatry Branch (formerly Adult Psychiatry Branch), NIMH, Bethesda, Maryland
 1977 - 1981 Deputy Clinical Director, Division of Clinical and Behavioral Research, NIMH, Bethesda, Maryland
 1981 - 1982 Acting Director, Intramural Research Program, NIMH, Bethesda, Maryland
 1982 - 1991 Chairman of Department of Psychiatry, School of Medicine, University of California, Irvine
 1982 - Present Professor, Department of Psychiatry, School of Medicine, University of California at Irvine
 1991 - 1998 Director of Research, Department of Psychiatry, School of Medicine, University of California, Irvine
 1985 - Present Distinguished Professor, Department of Psychiatry, School of Medicine, University of California, Irvine
 1995 Della Martin Chair, Psychiatry
 1998 – 2007 Academic Co-Chairman, Department of Psychiatry and Human Behavior, School of Medicine, University of California, Irvine
 2007 - 2010 Senior Associate Dean for Research, School of Medicine, University of California, Irvine

2010 - present Distinguished Professor, Associate Dean for Research Administration
MILITARY SERVICE

1960 - 1962 Commissioned Officer, USPHS
 1974 - 1981 Commissioned Officer, USPHS
 1982 - Present Commissioned Officer, Reserves, USPHS

PROFESSIONAL SOCIETIES

Institute of Medicine (IOM) of the National Academy of Sciences

Lifetime National Associate of the National Academies

American College of Neuropsychopharmacology (ACNP) (Life Fellow)

Collegium Internationale Neuro-Psychopharmacologicum (CINP) (Fellow)

American Psychiatric Association (Distinguished Life Fellow)

Psychiatric Research Society (Fellow)

Society for Neuroscience

NATIONAL SCIENTIFIC ADVISORY BOARDS

1987 - Present National Alliance for Research in Schizophrenia and Depression (NARSAD),
 (Brain and Behavior Research Foundation)
 1987 - 2003 Depression and Bipolar Support Alliance DBSA (formerly the
 National Depressive and Manic-Depressive Association NDMDA)
 1993 - 1995 Extramural Science Advisory Board, National Institute of Mental Health
 1997 - 2002 Governing Board of the WCBR Neuroscience Organization
 1997 - 2004 Nancy Pritzker Depression Network Scientific Advisory Board
 1997 - 1998 NIMH Scientific Advisory Group for the Extramural Research Division
 1997 - 2003 Scientific Advisory Board for the National Autism Society
 1997 - Present Scientific Advisory Board for the Harvard International Brain Repository
 2012 – 2013 National Action Alliance for Suicide Prevention (NAASP) Research
 Prioritization
 Task Force (RFP), Overview Expert Panel

NATIONAL ACADEMY OF MEDICINE (formerly the Institute of Medicine (IOM) / **NATIONAL
 ACADEMY OF SCIENCES**

- 1990 - 1994 Appointed Co-Chair, Division of Biobehavioral Sciences and Mental Disorders Board
- 1997 Appointed by President of the IOM to Chair a Study requested by the Commissioner of the FDA
- 1997 - 2003 Appointed by the President of the NAS to the Advisory Board for the National Academies Corporation
- 1998 - 2001 Appointed to Neuroscience and Behavioral Health Board, IOM
- 2001 Designated Lifetime National Associate of the National Academies
- 2003 - 2007 Appointed Executive Vice President, National Academies Corporation
- 2009 – 2010 Appointed Chairman of the Interest Group for Neuroscience, Behavior, Brain Function and Disorders

NATIONAL AWARDS

- 1969 APA Hofheimer Research Award -- Honorable Mention
- 1970 First Place Research Award from the Division of Psychopharmacology of the American Psychological Association
- 1970 Rush Gold Medal Award, American Psychiatric Association
- 1971 APA Hofheimer Research Award -- First Place
- 1971 DHEW Superior Service Award
- 1976 The McAlpin Mental Health Association Research Achievement Award
- 1977 Taylor Manor Hospital Psychiatric Award
- 1977 Public Health Service, Distinguished Service Medal
- 1997 Exemplary Psychiatrist Award, (NAMI)

- 2001 Nola Maddox Falcone Prize for Outstanding Achievement in Affective Illness Research (NARSAD)
- 2007 Earl Usdin Research Award, West Coast College of Biological Psychiatry (WCCBP)
- 2008 1st Annual Chair Achievement Award at the Psychiatric Chairs Summit
- 2013 Yale Psychiatry Distinguished Alumni Award
- 2015 The Payne Whitney Clinic Award for Extraordinary Public Service, The Department of Psychiatry, Weill Medical College of Cornell University, New York-Presbyterian Hospital

INTERNATIONAL AWARDS, HONORS, APPOINTMENTS, AND OTHER SCIENTIFIC RECOGNITION

- 1971 International Anna-Monika Award for Psychiatric Research First Place
- 1976 - 1989 Appointed Member of Committee of the Biological Psychiatry Section, World Psychiatric Association
- 1978 - Present Appointed Member of Section Committee on Pharmacopsychiatry, World Psychiatric Association
- 1984 - Present Appointed Member of the WHO Expert Panel on Mental Health
- 1984 – 1995 University of California, Irvine, Department of Psychiatry selected by the World Health Organization as the U.S. Collaborating Center for Research and Training in Biological Psychiatry (co-Director)
- 1986 - 1989 Appointed to Scientific Advisory Board, Max Planck Institute for Psychiatry
- 1990 - 2004 Appointed Chair, Corresponding Internationale Organisations Committee, CINP
- 1994 - 1998 Appointed Chair, Presidents Committee, CINP
- 2004 – Present Consulting Fellow, World Innovation Foundation (F.W.I.F.)

- 2011 The Rhoda and Bernard Sarnat International Prize in Mental Health, Institute of Medicine / National Academy of Sciences (IOM/NAS)
- 2012 The Pioneer Award, Collegium Internationale Neuro-Psychopharmacologicum (CINP)
- 2014 Paul Hoch Award, American College of Neuropsychopharmacology

SCIENTIFIC RECOGNITION

Listed as one of the 1,000 most frequently cited researchers from all fields of science from 1965 to 1980. Only four other psychiatrists were listed among the 1,000 researchers.

Listed as one of 250 of the most cited researchers in the world in the field of psychiatry/psychology (2000-2005) by ISI Thompson Scientific, the independent firm which catalogs and distributes scientific literature worldwide and compiles the index.

2015 - Total citations of all papers 34,843 (Source: Google Scholar)
H-Factor score of 103 (103 papers cited over 103 times, 55 of which were cited between 200 and 1219 times.)

ELECTED POSITIONS IN SCIENTIFIC SOCIETIES

- 1964 Member of Executive Council, American Psychosomatic Society
- 1974- 1975 President, Psychiatric Research Society
- 1980 Vice President, American College of Neuropsychopharmacology
- 1983 Founding President, West Coast College of Biological Psychiatry
- 1983 - 1984 President, American College of Neuropsychopharmacology (ACNP)
- 1986 - 1988 President, Collegium Internationale Neuropsychopharmacologicum (CINP)
- 1997 Governing Board of WCBR Neuroscience Organization
- 1998 Trustee, Association for Research in Nervous and Mental Disease

RESEARCH AWARD COMMITTEE MEMBERSHIP

- 1989 Janssen Award of the Collegium Internationale Neuropsychopharmacologicum (CINP)
- 1987 - 2004 Lieber Schizophrenia Research Award Committee of the Brain and Behavior Research Foundation (NARSAD)
- 2004 – Present Chair, Lieber Schizophrenia Research Award Committee, Brain and Behavior Research Foundation (NARSAD)

- 1992 - 1997 Member, Rhoda and Bernard Sarnat Award Committee for the International Prize in Mental Health, Institute of Medicine, National Academy of Sciences
- 1997 – 2008 Chair, Rhoda and Bernard Sarnat Award Committee for the International Prize in Mental Health, Institute of Medicine, National Academy of Sciences
- 1998 - Present Lieber Depression Award Committee, Brain and Behavior Research Foundation

UNIVERSITY OF CALIFORNIA (UCI) HONORS AND AWARDS

- 1985 Research Associates Award for Outstanding Professor, UCI
- 1986 Awarded title of Distinguished Professor, UCI
- 1989 UCI Professional Achievement Award (Lauds and Laurels)
- 1990 UCI Outstanding Researcher Award, (Lauds and Laurels)
- 1995 Appointed Della Martin Chair, Psychiatry

SELECTED COMMITTEES, UNIVERSITY OF CALIFORNIA AT IRVINE

- 1983 - 1991 Chairman, Strategic Planning Committee for School of Medicine
- 1985 Member, Search Committee for Dean of School of Medicine
- 1991 - 1996 Member, Advisory Board Bren Fellows Program
- 1993 - 1998 Member, Academic Resource Allocation Committee
- 1993 Member, Search Committee, Chair Department of Biological Chemistry
- 1991 - Present Ad-Hoc University Academic Review Committees
- 1994 - 1996 Chairman, Executive Vice Chancellor's Neuroscience Planning Task Force
- 2007 - 2011 Chairman, Dean's Research Advisory Committee
- 1998 - 2012 Chairman, Scientific Advisory Board, UCI Center for Cancer Genetics Research and Prevention
- 2003 Chairman, Search Committee, Director of the Beckman Laser Institute
- 2003 – Present Member, UCI Distinctions Committee
- 2015 -2017 Elected Member, SOM/COHS Representative Assembly (Academic Senate)

COMMITTEES, STATE OF CALIFORNIA

- 1985 - 1995 Appointed member of the Scientific Advisory Board to the Department of Mental Health
- 1985 - 1989 Appointed Director of the Mental Health Forum
- 1990 - 1996 Appointed member of the Joint Committee on Mental Health Research

EDITORIAL POSITIONS (CURRENT and PAST)

American Journal of Psychiatry, Associate Editor
Journal of Psychiatric Research, Member of Editorial Board
Psychiatric Annals, Editorial Consultant
Psychiatry Research, Member of Editorial Board
Substance and Alcohol Actions/Misuse, Member of Editorial Advisory Board
Human Neurobiology, Member of Editorial Board
Neurochemistry International, Member of Editorial Board
Integrative Psychiatry, Member of Editorial Board
Journal of Neurotransmission, Member of Advisory Board
The Neuroscientist, Associate Editor
Journal of Psychiatry and Neuroscience, International Editorial Advisory Board
Schizophrenia Research, Member of Editorial Board
Neuropsychopharmacology, Member of Editorial Board
International Journal of Neuropsychopharmacology, Member of Editorial Board
Experimental Neurology, Member of Editorial Board
Schizophrenia Bulletin, Member of Editorial Board
Clinical Neuroscience Research, ARNMD Journal, Editor-in-Chief
Psychiatry, Member of Editorial Advisory Board
Open Psychiatry Journal, Member of Editorial Board

CLUBS

1982 Elected to membership in the Cosmos Club, Washington, D.C.

MAJOR RESEARCH INTERESTS

Major research interests involve clinical psychobiological studies of manic-depressive illness, schizophrenia and childhood mental illness. These include behavioral studies, studies of the efficacy and mode of action of psychopharmacological agents, brain imaging, molecular genetic studies, neuropathological studies and investigations of brain circuitry abnormalities, which may be related to the major psychoses.

ADMINISTRATIVE EXPERIENCE

1966 - 1971 Chief of psychobiological research group. Coordinated research on affective disorders and developed and directed clinical care program on two psychiatric wards in the Clinical Center, NIMH.

1971 - 1973 Director, Division of Narcotic Addiction and Drug Abuse, NIMH: involved coordinating much of the effort in drug abuse for the Department of Health, Education and Welfare as a designated lead agency in drug abuse for HEW. This included rehabilitation, training, education, research and international drug abuse health programs. The position further involved administratively supervising the

Lexington Research Center, preparing and testifying before Congressional committees concerning requests for budget appropriations and legislation concerning drug abuse. During my time as Director of the Division, I increased treatment facilities, research, and training efforts in the U.S. A national health care delivery system for the narcotic addict and drug abuser was established with an increase in treatment centers from 23 to 140 centers. Eight university-based research centers in drug abuse were established and the number of individual clinical investigators receiving grants increased from 44 to 130. The budget of the Division during this three-year period of time increased from 60 million to 244 million dollars. The permanent staff size of the Division in 1973 was 793.

1973 - 1977 Chief, Adult Psychiatry Branch, NIMH, Bethesda, Maryland

1977 - 1981 Deputy Clinical Director, Division of Clinical and Behavioral Research, NIMH, Bethesda, Maryland.

1977 - 1981 Chief, Biological Psychiatry Branch (formerly Adult Psychiatry Branch), NIMH, Bethesda, Maryland: Coordinated Psychobiological Research Program on affective illness, schizophrenia, drug abuse and childhood mental illness. Program included investigations into the psychogenetics of depression, and sleep, utilizing positron emission tomography (PET). The Biological Psychiatry Branch also developed a basic research component in biochemistry and pharmacology.

Served as Chairman, Clinical Investigations Coordinating Committee for Clinical Intramural Research, NIMH, Bethesda, Maryland.

1982 - 1991 Chairman, Department of Psychiatry, School of Medicine, University of California at Irvine. Reorganized teaching program; developed research program in biological psychiatry; increased peer reviewed and other grant monies for research 20-fold; developed clinical research units; developed international research collaborations; initiated and assisted in the first agreement between a private industry and the University of California resulting in the current Joan Irvine Smith Facility. It included a facility for the Department of Psychiatry Brain Imaging Program; acquired PET scanner and cyclotron for the Department of Psychiatry; established Department of Psychiatry as the U.S. Center for Research and Training in Biological Psychiatry of the World Health Organization; initiated and helped obtain \$19 million in state funds for the Neuropsychiatric Hospital and Research Center (opened in 1994).

1991- 1998 Director of Research, Coordinates research efforts in Department of Psychiatry. Between 1990-1995, the Department of Psychiatry ranked #1 out of the 23 basic and clinical departments in the UCI School of Medicine in terms of NIH/NSF Extramural Research Funding per Year/Per FTE.

1998- 2007 Academic Co-Chairman of the Department of Psychiatry, School of Medicine, University of California, Irvine. The AAMC annually ranks all Departments of all medical schools on a number of criteria including total research dollars per fulltime

faculty. For the last 3 years, the Department of Psychiatry at UCI has ranked in the top 5% of the 123 medical schools and ranked #1 of the 72 publicly-funded medical schools.

2007 – 2010 Senior Associate Dean for Research, School of Medicine

2010-present Associate Dean for Research Administration

TEACHING EXPERIENCE

- 1958 - 1959 Teaching Assistant in Psychiatry, Yale University School of Medicine, New Haven, Connecticut.
- 1967 - 1981 Organized and conducted weekly teaching seminars on behavioral and biological aspects of psychiatric research, NIMH.
Organized and conducted monthly clinical grand rounds, NIMH.
Organized distinguished guest lecture series, NIMH.
Organized and conducted weekly journal review, NIMH.
Conducted monthly evening teaching sessions on research methodology, NIMH.
Organized and conducted research teaching session for private psychiatrists in the Washington Metropolitan area.
- 1982 - 1991 Conducted seminars and presented lectures at University of California, Irvine.
Supervised organization of psychiatric training program for 400 medical students and 63 psychiatric residents.
Reorganized core curriculum for residents; initiated research thesis requirements.
- 1997-2006 Developed and taught new course in Molecular Genetics for Faculty and Residents
- 1991-Present Lectures to medical students, residents, and faculty. Conducts research seminars.

SELECTED INTERNATIONAL CONSULTATIONS AND LECTURES

- | | |
|-------------------------|---|
| Rio de Janeiro, Brazil. | Consultant to the President's Commission on Drug Abuse. |
| Mexico City, Mexico. | Consultant to the President's Commission on Drug Abuse. |
| Brussels, Belgium. | Member of the U.S. Delegation to Committee on Challenges of Modern Society of the North Atlantic Treaty Organization (NATO) |
| Bogota, Columbia. | Official U.S. representative and consultant to First National Conference on Drug Abuse |
| Bellagio, Italy. | HEW Consultant to conference on "The Need and |

Opportunities for Work by Foundations in the Drug Field"

- Copenhagen, Denmark. Invited to organize and chair symposium at Collegium Internationale Neuro-Psychopharmacologicum (CINP) on "Biological Studies of Affective Disorders"
- Newcastle-on-Tyne, England Invited Lecturer, Royal Victoria Infirmary and University, Department of Psychological Medicine
- Birmingham, England Invited Lecturer, Birmingham University, Department of Psychological Medicine
- Stockholm, Sweden Invited Lecturer, Karolinska Institute
- September, 2007 Invited Lecturer
Weill Medical College of Cornell University,
Department of Psychiatry
"Metabolic and signaling pathways dysregulated in bipolar disorder and schizophrenia."
- June 2011 Invited Lecturer - The Daniel X Friedman Memorial Lecture
Simmel Institute for Neuroscience and Human Behavior, UCLA
"Rapid Acting Antidepressant Strategies: Chronotherapeutic Research and Practical Application"
- October 2011 Invited Lecturer - Meet the Scientist / Webinar
Brain and Behavior Research Foundation (formerly NARSAD)
"Rapid-Acting Antidepressant Strategies"

<http://www.youtube.com/watch?v=L0cHxpVZxZs&feature=youtu.be>

- Peking, China Invited Lecturer, 3rd Peking Hospital
Shanghai, China Invited Lecturer, Shanghai Psychiatric Hospital
Bombay, India Invited Lecturer
Lucknow, India Invited Lecturer
New Delhi, India Invited Lecturer

Plus over 160 others

World Health Organization (WHO)

Served as a WHO United States Representative during planning conferences for collaborative international research in Biological Psychiatry at the following locations:

Moscow, USSR

Copenhagen, Denmark
Munich, West Germany
Sapporo, Japan
Basel, Switzerland

ADDITIONAL INFORMATION

Listed on 19 Patents

12/23/19

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3. Bunney WE Jr. Some observations on depressive reactions in college students. *Proc Third World Congress of Psychiatry, Univ of Toronto Press/McGill University Press, 1961, pp. 1225-1230.*
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10. Bunney WE Jr, Fawcett JA. Possibility of a biochemical test for suicidal potential. An analysis of endocrine findings prior to three suicides. *Arch Gen Psychiatry* 13:232-239, 1965.
11. Bunney WE Jr, Davis JM. Norepinephrine in depressive reactions. *Arch Gen Psychiatry* 3. 483-494, 1965.
12. Bunney WE Jr. Biochemical theories of depression. A challenge for progress through cooperative research. *Proceedings of the IV World Congress of Psychiatry, 1966, p. 133.*
13. Bunney WE Jr, Fawcett JA. 17-Hydroxycorticosteroid excretion prior to severe suicidal behavior. *Proc. IV International Conference for Suicide Prevention, 1967, pp. 128-139.*

14. Bunney WE Jr, Davis JM, Weil-Malherbe H, Smith ERB. Biochemical changes in psychotic depression. *Arch Gen Psychiatry* 16.448-460, 1967.
15. Fawcett JA, Bunney WE Jr. Pituitary adrenal function and depression. An outline for research. *Arch Gen Psychiatry* 16.517-535, 1967.
16. Colburn RW, Goodwin FK, Bunney WE Jr, Davis JM. Effect of lithium on the uptake of noradrenaline by synaptosomes. *Nature* 215.1395-1398, 1967.
17. Davis JM, Goodwin FK, Bunney WE Jr, Murphy DL, Colburn RW. Effects of ions on uptake of norepinephrine by synaptosomes. *The Pharmacologist* 9.184, 1967.
18. Bunney WE Jr, Fawcett JA. Biochemical research in depression and suicide. In: Resnik, HLP (Ed.). *Suicidal Behaviors*. Boston, Massachusetts. Little, Brown and Company, 1968, pp. 144-159.
19. Bunney WE Jr. Biochemical factors in psychotic depressions. In: Rupp, C. (Ed.). *Mind as a Tissue*. New York, New York. Harper & Row Publishers, Inc., 1968, pp. 196-213.
20. Colburn RW, Goodwin FK, Murphy DL, Bunney WE Jr, Davis JM. Quantitative studies of norepinephrine uptake by synaptosomes. *Biochem Pharmacol* 17.957-965, 1968.
21. Bunney WE Jr, Goodwin FK, Davis JM, Fawcett JA. A behavioral-biochemical study of lithium treatment. *Am J Psychiatry* 125.91-104, 1968.
22. Bourne HR, Bunney WE Jr, Colburn RW, Davis JM, Davis JN Shaw DM, Coppen A. Noradrenaline, 5-hydroxytryptamine, and 5-hydroxyindoleacetic acid in hindbrains of suicidal patients. *Lancet* 2.805-808, 1968.
23. Greenspan K, Goodwin FK, Bunney WE Jr, Durell J. Lithium ion retention and distribution. Patterns during acute mania and normothymia. *Arch Gen Psychiatry* 19.664-673, 1968.
24. Bunney WE Jr, Fawcett JA, Davis JM, Gifford S. Further evaluation of urinary 17hydroxycorticosteroids in suicidal patients. *Arch Gen Psychiatry* 21.138-150, 1969.
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INVITED CO-EDITORSHIP

1. William E. Bunney, Jr., Jack Barchas: *Clinical Neuroscience. Manic Depressive Illness* (two issues co-editors) 1994.
2. William E. Bunney, Jr., Herbert Y. Meltzer: *Clinical Neuroscience. Schizophrenia* (one issue co-editors) 1995.

LAY ARTICLE

Bunney BG, Bunney WE. "Future directions and prospects for psychiatric research and implications for clinical care." *NARSAD Research Newsletter*, Vol. 16, Issue 2, Pages 8-10 (Summer 2004)

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INSTITUTE OF MEDICINE, NATIONAL ACADEMY OF SCIENCE REPORTS

1. "Neurological, Psychiatric and Developmental Disorders, Meeting the Challenge in the Developing World," Committee on Nervous System Disorders in Developing Countries, Institute of Medicine Board on Global Health, Jablensky A, Johnson R, Bunney WE, Cruz M, Durkin M, Familusi J, Gourie-Devi M, Jamison D, Jenkins R, Kaaya S, Kleinman A, McGuire T, Murthy RS, Silverberg D, Ustun B. National Academy Press, 2001.
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APPENDIX 2: Scientific contributions of WILLIAM E. BUNNEY, JR.

I. Service to Medical Profession

Dr. William Bunney served the scientific community in leadership roles in major societies, on Editorial Boards and on NIH Study Sections. Dr. Bunney was elected to and served as President of three societies.

Elected Positions In Scientific Societies

1974- 1975	President, Psychiatric Research Society
1983 - 1984	President, American College of Neuropsychopharmacology
1986 - 1988	President, Collegium Internationale Neuropsychopharmacologicum (CINP)

Dr. William Bunney has held a number of administrative positions during his career including:

Director of the Division of Narcotic Addiction and Drug Abuse

Dr. Bunney's Division restructured the Federal Drug Abuse program in the United States. Historically, in the 1960s and 1970s, there was a strikingly inadequate health care delivery system for narcotic addicts and drug abusers, and there was relatively little research in this critical area. In 1971 Dr. Bunney was appointed by the Secretary of the Department of Health and Human Services to the position of Director of the Division of Narcotic Addiction and Drug Abuse. This included rehabilitation, training, education, research and international drug abuse health programs. The position further involved administratively supervising the Lexington Research Center, preparing and testifying before Congressional committees concerning requests for budget appropriations and legislation related to drug abuse. During this time, Dr. Bunney's Division increased treatment facilities, research, and training efforts in the U.S. A national health care delivery system for the narcotic addict and drug abuser was established with an increase in treatment centers from 23 to 140 centers. Eight university-based research centers in drug abuse were created and the number of individual clinical investigators receiving grants increased from 44 to 130. The budget of the Division during his three-year tenure increased from \$60 million to \$244 million dollars. The permanent staff size of the Division in 1973 was 793.

Establishment of the First Childhood Psychiatric Disorders Branch at the NIMH

At the NIMH, Bunney advocated for and established the first Branch of the Intramural Program dedicated to the biological and genetic studies of childhood psychiatric disorders. The Branch is internationally recognized as an important contributor to child mental health and includes studies of ADHD, autism, depression and childhood onset schizophrenia.

Service on Editorial Boards and to Society

In the past and currently, Dr. Bunney served in various Editorial positions on 19 scientific journals. He served on and chaired Study Sections for the NIMH, served on three International Prize Committees, and on the Scientific Advisory Boards of National and International organizations.

Service to the National Academy of Medicine

Dr. Bunney chaired and organized projects for the National Academy of Medicine, including a study titled, "Reducing Suicide: a National Imperative." One recommendation from the study was to establish national centers for the prevention and investigation of suicide. Five new Centers were funded by the NIMH.

Service to the Brain and Behavior Research Foundation

Dr. Bunney currently serves on the Scientific Council for the Brain and Behavior Research Foundation, which since 1987 has awarded over 3,497 grants for an overall investment of \$204.4 million, to Young Investigators conducting research across 100 institutions in 13 countries.

Service on National Scientific Advisory Boards

1987 - Present	Brain and Behavior Research Foundation (formerly National Alliance for Research in Schizophrenia and Depression, NARSAD)
1987 - 2003	Depression and Bipolar Support Alliance DBSA (formerly the National Depressive and Manic-Depressive Association NDMDA)
1993 - 1995	Extramural Science Advisory Board, National Institute of Mental Health
1997 - 2004	Nancy Pritzker Depression Network Scientific Advisory Board
1997 - 1998	NIMH Scientific Advisory Group for the Extramural Research Division
1997 - 2003	Scientific Advisory Board for the National Autism Society
1997 - Present	Scientific Advisory Board for the Harvard International Brain Repository
2012 - 2013	National Action Alliance for Suicide Prevention (NAASP) Research Prioritization Task Force (RFP), Overview Expert Panel

Service to International Scientific Community

1984 - Present	Appointed Member of the World Health Organization (WHO) Expert Panel on Mental Health
1984 - 1995	University of California, Irvine, Department of Psychiatry selected by the World Health Organization as the U.S. Collaborating Center for Research and Training in Biological Psychiatry (co-Director)
1986 - 1989	Appointed to Scientific Advisory Board, Max Planck Institute for Psychiatry

II. Biomedical Research Accomplishments

Selected Investigations from 447 Peer-Reviewed Papers

Initiated Patient Research Ward at NIMH

Early in his career Dr. Bunney developed an Intramural Program at the NIMH, under the mentorship of Dr. David Hamburg. The ward, the first of its kind, included 24hour behavioral ratings of patients and daily collection of body fluids. The unit set an internationally acclaimed model for the intensive study of neuropsychiatric disorders and provided the ability to obtain a new quality of behavioral and biological data (*Archives of General Psychiatry*, 1963).

Lithium and the Treatment of Bipolar Disorder

Research made possible by the methodology in this unit involved early double-blind studies of lithium treatment where placebo was substituted for lithium in an on-off longitudinal design. Over 5 days, the blind daily ratings documented the time-course of a consistent step-wise decrease in manic ratings in patients on lithium and an increase in manic ratings on placebo. This work provided irrefutable evidence of the efficacy of lithium during a manic episode.

Dr. Bunney's research helped launch the use of lithium in the United States. He played a role in the FDA approval of the use of lithium in bipolar disorder and was a member of the APA Task Force report on the status of lithium which was a key document in the FDA approval process (*Am J Psychiatry* 1975). Now more than 4 decades later, lithium is one of the most widely used treatments for mood disorders and has benefited millions of patients.

Investigations on the Mode of Action of Lithium

Ongoing research has contributed significant data concerning potential mechanisms of action of lithium treatment. Below are listed four papers which contributed to this body of knowledge. Research on Lithium was shown to alter the uptake of noradrenaline by synaptosomes (*Nature* 1967). Follow-up preclinical investigations under the supervision of Bunney at the NIMH reported lithium's effects on subjective functioning and morphine-induced euphoria (*Science* 1977). Further research showed that lithium blocked haloperidol-induced presynaptic dopamine supersensitivity (*Nature* 1978) and also that chronic lithium prevented dopamine receptor supersensitivity (*Science* 1978).

- a) Colburn RW, Goodwin FK, Bunney WE Jr, Davis JM. Effect of lithium on the uptake of noradrenaline by synaptosomes. *Nature* 215.1395-1398, 1967.
- b) Jasinsky DR, Nutt JG, Haertzen CA, Griffith JD, Bunney WE Jr. Lithium. Effects on subjective functioning and morphine-induced euphoria. *Science* 195.582-584, 1977.
- c) Gallager DW, Pert A, Bunney WE Jr. Haloperidol-induced presynaptic dopamine supersensitivity is blocked by chronic lithium. *Nature* 273.309-312, 1978.
- d) Pert A, Rosenblatt JE, Sivit C, Pert CB, Bunney WE Jr. Long-term treatment with lithium prevents the development of dopamine receptor supersensitivity. *Science* 201.171-173, 1978.

Biomarkers for Suicide

Dr. Bunney made significant contributions to research for biomarkers of suicide. In the United States 40,000 individuals commit suicide each year. The World Health Organization estimates that 1 million commit suicide worldwide each year. Thus the accurate identification of risk of suicidal behavior is a critical global imperative. The NIMH research ward facilitated the investigation of suicidal patients.

Over 200 severely depressed, intensely suicidal patients were evaluated longitudinally throughout their hospitalization. Behavioral ratings using the Bunney-Hamburg rating scale were completed hourly. Daily evaluations of urinary 17-hydroxycorticosteroids (17-OHCS), the major breakdown product of cortisol, were obtained. Extreme elevations of 17-OHCS were found to be a reliable biomarker of severe suicidal behavior including completed suicides (*Archives of General Psychiatry*, 1965; More recently, Dr. Bunney and his colleagues published a scale to assess psychological pain as a reliable predictor of suicidal intent. Bunney's research team also published data showing that 2 additional biomarkers, metallothioneins and polyamines represent risk factors in the evaluation of suicidal behavior.

In 2012-2013 Bunney was selected to serve on an Overview Expert Panel for the National Action Alliance for Suicide Prevention, Health and Human Services (HHS) National Action Alliance for Suicide Prevention,

Research Prioritization Task Force. This task force produced a comprehensive publication and recommendations, which were approved by HHS and by the White House.

Innovative Norepinephrine Hypothesis

Bunney published a report presenting evidence that norepinephrine was critical in the pathophysiology of depressive reactions (*Arch Gen Psychiatry* 1965). This landmark high-impact paper was labeled a Citation Classic and has been cited over 1200 times, including recent citations. Along with a review by Schildkraut (1965), the norepinephrine hypothesis stimulated hundreds of scientific efforts.

One of these scientific studies involved MHPG (3-methoxy-4-hydroxyphenylglycol), the major metabolite of norepinephrine. MHPG was assayed in cerebrospinal fluid of mood disorder patients and was found to be lower in depressed patients compared to controls, which is compatible with altered norepinephrine metabolism (*Science* 1973). Research on alpha-methyl-para-tyrosine, the rate limiting step in the synthesis of dopamine, and on L-Dopa provided evidence implicating norepinephrine in depressive disorders.

- a) Bunney WE Jr, Davis JM. Norepinephrine in depressive reactions. *Arch Gen Psychiatry* 3:483-494, 1965.
- b) Post RM, Gordon EK, Goodwin FK, Bunney WE Jr. Central norepinephrine metabolism in affective illness. MHPG in the cerebrospinal fluid. *Science* 179:1002-1003, 1973.

First Direct Evidence of Circadian Patterns of Gene Expression in Human Brain and Abnormal Patterns in Major Depressive Disorder

A subset of patients with major depressive disorder (MDD) frequently experience abnormal 24 hour rhythms in sleep, temperature, hormonal secretions, and mood. These rhythms are all controlled by circadian clock genes. In 2000 Bunney (WE) and Bunney (BG) reviewed molecular clock gene machinery in man and hypothesized that core circadian clock genes could be disrupted in depressive disorders.

In 2013, a major collaborative study on which Bunney was one of the PIs was supported by the Pritzker Neuropsychiatric Disorders Research Fund, The study reported the first direct evidence of significant sinusoidal rhythms that varied in synchrony over 24 hours across six human brain areas in nonpsychiatric controls. These rhythms were significantly disrupted in major depressive disorder patients, most significantly in the anterior cingulate.

Dr. Bunney's role in this research involved an ongoing focus on circadian clock genes, participation in the analysis of the data, and in the preparation of the manuscript. Findings from this research provide clues for potentially important and unique molecular targets for the treatment of MDD. Recently, Bunney received information from the PNAS journal stating that Altmetric, a service that tracks downloads reported that out of 38,131 articles tracked from PNAS, this paper ranked in the top 98%.

First evidence to suggest that rapid-acting antidepressants may act on Clock Genes

Bunney and Bunney also proposed that rapid treatments for depression including sleep deprivation therapy and low dose IV ketamine might function in part by resetting abnormal circadian clock genes. The first paper to support this suggestion was published in 2011, where it was shown that ketamine significantly altered clock genes in neuronal cell culture (Bellet, et al. 2011).

- a. Bunney WE, Bunney BG. Molecular clock genes in man and lower animals: Possible implications for circadian abnormalities in depression. *Neuropsychopharmacology*, 22 (4): 335-345, (2000).

- b. Bellet MM, Vawter MP, Bunney BG, Bunney WE, Sassone-Corsi P. Ketamine Influences CLOCK:BMAL1 Function Leading to Altered Circadian Gene Expression. PLoS ONE 11-13223R1 10.1371/journal.pone.0023982. Aug 2011.
- c. Li JZ, Bunney BG, Meng F, Hagenauer MH, Walsh DM, Vawter MP, Evans SJ, Choudary PV, Cartagena P, Barchas JD, Schatzberg AF, Jones EG, Myers RM, Watson SJ, Akil H, Bunney WE. Circadian patterns of gene expression in the human brain and disruption in major depressive disorder. PNAS / doi:10.1073/ PNAS 1305814110, May 2013.
- d. Bunney BG, Li JZ, Walsh DM, Stein R, Vawter MP, Cartagena P, Barchas JD, Schatzberg AF, Myers RM, Watson SJ, Akil H, Bunney WE. Circadian dysregulation of clock genes: clues to rapid treatments in major depressive disorder. *Molecular Psychiatry* (2015) 1 - 8;1359-4184/14.

III. National and International Awards and Recognition

National Academies

- 1988 Elected to the National Academy of Medicine
- 2001 Designated by the President of the National Academies, the honorific title of "Lifetime National Associate of the National Academies"
- 2003 -- 2007 Appointed for a term as Executive Vice President, National Academies Corporation
- 2009 – 2010 Appointed Chairman of the Interest Group for Neuroscience, Behavior, Brain Function and Disorders

National Awards

- 1970 First Place Research Award from the Division of Psychopharmacology of the American Psychological Association
- 1971 APA Hofheimer Research Award -- First Place
- 1971 DHEW Superior Service Award
- 1976 The McAlpin Mental Health Association Research Achievement Award
- 1977 Public Health Service, Distinguished Service Medal
- 1998 Exemplary Psychiatrist Award, (NAMI)
- 2001 Nola Maddox Falcone Prize for Outstanding Achievement in Affective Illness Research (Brain and Behavior Research Foundation)
- 2008 1st Annual Chair Achievement Award at the Psychiatric Chairs Summit
- 2013 Yale Psychiatry Distinguished Alumni Award
- 2014 Paul Hoch Award, American College of Neuropsychopharmacology 2015 The Payne Whitney Clinic Award for Extraordinary Public Service, The Department of Psychiatry, Weill Medical College of Cornell University

International Awards

- 1971 International Anna-Monika Award for Psychiatric Research First Place
- 2011 Awarded the Highly Prestigious *Rhoda and Bernard Sarnat International Prize in Mental Health*, from the National Academy of Medicine / National Academy of Sciences (NAM/NAS). Previous honorees include two scientists who went on to receive the Lasker Award; two researchers who received the Medal of Freedom, the highest civilian honor, from the President of the United States; and one investigator who was

knighted by the Queen of England for his research. Bunney received this award for his lifetime contributions to research. It was announced to the Membership of the National Academy of Medicine at their annual meeting and was presented to Bunney by the President of the National Academy of Medicine at a special ceremony.

2012 The Pioneer Award, Collegium Internationale Neuro-Psychopharmacologicum (CINP)

IV. Additional Relevant Recognition

Scientific Recognition

Listed as one of the 1,000 most frequently cited researchers from all fields of science from 1965 to 1980. Only four other psychiatrists were listed among the 1,000 researchers.

Listed as one of 250 of the most cited researchers in the world in the field of psychiatry/psychology (2000-2005) by ISI Thompson Scientific, the independent firm which catalogs and distributes scientific literature worldwide and compiles the index.

2015 - Total citations of all papers 34,843 (Source: Google Scholar)
H-Factor score of 103

(103 papers cited over 103 times, 55 of which were cited between 200 and 1219 times.)